CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761040Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	August 8, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Mate Tolnay, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761040
Product:	Besponsa (inotuzumab ozogamicin)
Applicant:	Wyeth Pharmaceuticals Inc.
Submission Date(s):	December 20, 2016, April 19, 2017, June 15, 2017, and July 19, 2017, July 28, 2017, and August 7, 2017

I) RECOMMENDATION

The labels and labeling for Besponsa (inotuzumab ozogamicin) for Injection, 0.9 mg per vial single-dose vial submitted on July 19, 2017 (container label), July 28, 2017 (carton labeling) and August 7, 2017 (prescribing information) are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted the final portion of the rolling submission for BLA 761040 Besponsa (inotuzumab ozogamicin) on December 20, 2016. The Applicant submitted labels and labeling on December 20, 2016 and updated labeling on April 19, 2017 and June 15, 2017.

Table 1: Proposed Product Characteristics of Besponsa (inotuzumab ozogamicin).

Proprietary Name:	Besponsa
Nonproprietary Name:	Inotuzumab Ozogamicin
Dosage Form:	for Injection
Strength and Container-Closure:	0.9 mg per single-dose vial
Route of Administration:	intravenous infusion
Storage and Handling:	Store BESPONSA vials in the original carton. Refrigerate (2-8°C; 36-46°F) and protect from light (b) (4) Do not freeze. (b) (4) the solution should be protected from light. (b) (4) the solution should be used immediately or stored at room temperature (20-25°C; 68-77°F) or refrigerated (2-8°C; 36-46°F) for up to 3 hours. Do not freeze *[see Dosage*

	and Administration (2.3)]. During administration, the solution should be protected from light.
Indication:	a CD22-directed antibody-drug conjugate indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Dose and Frequency:	Administer BESPONSA intravenously by infusion over 1 hour. First Cycle: the recommended total dose of BESPONSA for all patients is 1.8 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2). Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves a complete remission (CR) or a complete remission with incomplete hematologic recovery (CRi), and/or to allow recovery from toxicity. Subsequent cycles: the recommended total dose of BESPONSA is 1.5 mg/m^2 per cycle, administered as 3 divided doses on Days 1 (0.5 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who achieve a CR or CRi or 1.8 mg/m^2 per cycle given as 3 divided doses on Days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2), and 15 (0.5 mg/m^2) for patients who do not achieve a CR or CRi. Subsequent cycles are 4 weeks in duration. For patients proceeding to hematopoietic stem cell transplant (HSCT), the recommended duration of treatment with BESPONSA is 2 cycles. A third cycle should be considered for those patients who do not achieve a complete remission (CR) or a complete remission with incomplete hematologic recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT (b) (4) additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment.

III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

At the Late Cycle Meeting on June 23, 2017, the applicant proposed to include statements in the labeling for (b) (4) the 0.9 mg (b) (4) the concentration of the reconstituted solution is 0.25 mg/mL. The applicant agreed that the labeled amount for the product is 0.9 mg. (b) (4)

In the July 19, 2017, submission, the Applicant expressed concern that prescribing physicians or dispensing pharmacists might incorrectly assume the concentration of the reconstituted inotuzumab ozogamicin solution is (b) (4) and subsequently inadvertently overdose the patient if the (b) (4) is not also clearly included in appropriate places in labeling. (b) (4)

We maintain that the labeling (b) (4) We are concerned that healthcare professionals (b) (4) stated in the labeling for one drug product resulting in prescribing and product preparation confusion. Healthcare professional rely on the labels and labeling to reflect information accurately to allow prescribing, preparation, administration of the appropriate dose to the patient. There are products on the market where there are differences between the diluent volume and the withdrawable volume for reconstituted drug products as well as different total content of lyophilized powder in the vial compared to the labeling claim. We determined from best labeling practices

that the critical information in the labeling for the healthcare professional to appropriately prepare the product includes the volume of diluent required for reconstitution, the concentration of the reconstituted solution, and the volume (mL) and amount of drug (mg) that can be withdrawn and administered from the vial after reconstitution. See recommendations for the container label, carton labeling, and prescribing information in Appendix C.

The Applicant requested to include (b) (4) in the labeling. We determined that the product be labeled with the deliverable volume that can be consistently pulled from the vial after reconstitution (3.6 mL). (b) (4) The Applicant revised as recommended.

The Applicant revised the recommended language in the prescribing information from using the word "deliverable" to using the word (b) (4). Per the guidance, the vial must state what can be withdrawn and administered and the word deliverable speaks to both (b) (4) The Applicant revised as recommended.

V) CONCLUSION

The prescribing information, container labels, and carton labeling for Besponsa (inotuzumab ozogamicin) for Injection, 0.9 mg per vial single-dose vial were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information [August 7, 2017]
- Container Labels [July 19, 2017]
- Carton Labeling [July 28, 2017]

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

Appendix B: Other

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10	x			
Manufacturer name, address, and license number 21 CFR 610.60		x		Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h (Pearl River, NY 10965) as follows: *Applicant on Form FDA 356h* *Address* *US License No. xxxx* Note that if the only manufacturer information on the labeling is the licensed manufacturer, then "Manufactured by" may be omitted to create space for other important information. Remove (b) (4) from the License No. statement. *The applicant stated that the product is manufactured under US License Number 003, held by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc, with a registered address in Philadelphia, PA. The manufacturer's address on the label and carton is consistent with the biologics labeling regulations. The Sponsor will revise the 356h form to reflect the registered Philadelphia address for license number 003*

[1] Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				so that it is consistent with the labeling. The "manufactured by" statement is consistent with the approved labeling for other biologic or vaccine products currently manufactured under license number 003.The Applicant's revision is acceptable.
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21CFR 201.100	x			
Expiration date 21 CFR 610.60 21 CFR 201.17	x			
Multiple dose containers (recommended individual dose) 21 CFR 610.60			x	
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	x			Relocate "Rx only" to appear at the top of the primary display panel (PDP) to allow for addition and prominence of other critical information on the PDP. *The Applicant's revision is acceptable.*
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10			x	
No container label 21 CFR 610.60			x	
Visual inspection 21 CFR 610.60		x		Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				The applicant responded that the vial label is attached to the vial (b) (4) *and is affixed using* (b) (4) *The vial label does not overlap on the vial; therefore, there is a content inspection area (label free-area) on the labeled vial as required by 21 CFR 610.60(e).The Applicant's response is acceptable.*
NDC numbers 21 CFR 201.2 21CFR 207.35	x			
Route of administration 21 CFR 201.5 21 CFR 201.100	x			
Preparation instructions 21 CFR 201.5		x		If space permits, add preparation instructions to the side panel including final concentration after reconstitution as follows: "Reconstitute with 4 mL Sterile Water for Injection, USP for a concentration of 0.25 mg/mL and further dilute." *Applicant responded that space does not permit.* As part of the labeling strategy discussed at the 23June17 Late Cycle meeting to address your concern that the end user may assume the concentration of the reconstituted vial is not 0.25 mg/mL, unbold the storage statement and revise the side panel to accommodate this information as follows: "Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do Not Freeze. See prescribing information for dosage, preparation, administration (b) (4) Concentration is 0.25 mg/mL when reconstituted with 4 mL Sterile Water for Injection (b) (4) *Applicant revised as requested.*
Package type term 21 CFR 201.5		x		Add the following statement to the primary display panel "Single-dose vial. Discard unused portion.". See Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				2015. *The Applicant's revision is acceptable.*
Drugs Misleading statements 21 CFR 201.6	x			
Strength 21 CFR 201.10 21CFR 201.100	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Bar code label requirements 21 CFR 201.25 21CFR 610.67	x			
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100		x		Revise the statement (b) (4) to read "See prescribing information for dosage, preparation and administration" *The applicant's revision is acceptable*
Inactive ingredients 21 CFR 201.100	x			Space considerations, see carton labeling.
Storage requirements	x			Revise the storage statement from (b) (4) to read "Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton. Do Not Freeze. (b) (4) (b) (4) *The Applicant revised as requested. However, see Late Cycle Meeting minutes dated 23June17, Discussion section, and preparation instruction comments to the applicant above for additional recommended revisions.*

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Dispensing container 21 CFR 201.100			x	

Package Label[5] Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			
Manufacturer name, address, and license number 21 CFR 610.61		x		Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h (Pearl River, NY 10965) as follows: Manufactured by: *Applicant on Form FDA 356h Address* *US License No. xxxx* Note Remove (b) (4) from the License No. statement. *The applicant stated that the product is manufactured under US License Number 003, held by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc, with a registered address in Philadelphia, PA. The manufacturer's address on the label and carton is consistent with the biologics labeling regulations. The Sponsor will revise the 356h form to reflect the registered Philadelphia address for license number 003 so that it is consistent with the labeling. The "manufactured by" statement is consistent with the approved labeling for other biologic or vaccine products currently manufactured under license number 003. The Applicant's revision is acceptable.*

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Lot number or other lot identification 21CFR 610.61	x			
Expiration date 21 CFR 610.61 21 CFR 201.17	x			
Preservative 21 CFR 610.61	x			
Number of containers 21 CFR 610.61			x	
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
Storage temperature 21 CFR 610.61		x		Revise the storage statement from (b) (4) to read "Refrigerate vial at 2°C to 8°C (36°F to 46°F) in original carton. Do Not Freeze. Protect from light during storage, preparation, and administration." *The Applicant revised as requested.*
Handling: "Shake Well", "Do not Freeze" or equivalent 21 CFR 610.61	x			
Multiple dose containers (recommended individual dose) 21 CFR 610.61			x	
Route of administration 21 CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Known sensitizing substances 21 CFR 610.61			x	
Antibiotics added during manufacturing 21 CFR 610.61			x	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100				Revise the list of ingredients by placing the inactive ingredients in alphabetical order per USP General Chapters: <1091> Labeling of Inactive Ingredients. Additionally, revise the amounts of ingredients based upon how much is delivered in x mL of reconstituted solution. For example: "Each single-dose vial delivers (b) (4) mg inotuzumab ozogamicin, polysorbate 80 (x mg), sodium chloride (x mg), sucrose (x mg), and tromethamine (x mg)". *The applicant added* (b) (4) *The Applicant's revision is not acceptable.* Per discussion at the 23June17 Late Cycle meeting on overfill and a proposed labeling strategy to address your concern that the end user may assume the concentration of the reconstituted vial is not 0.25 mg/mL, revise the side panel to accommodate this information as follows: "Each single-dose vial delivers 0.9 mg inotuzumab ozogamicin, polysorbate 80 (xx mg), sodium chloride (xx mg), sucrose (xx mg), and tromethamine (xx mg). (b) (4) Gently swirl the vial to aid dissolution. DO NOT SHAKE. (b) (4)

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				(b) (4) No U.S. standard of potency." *The Applicant responded to the Agency in the July 19, 2017 submission expressing concerns that the healthcare provider may assume the wrong concentration of the reconstituted solution* (b) (4) Revise the inactive ingredient information to consistently reflect the labeled strength of the drug product as previously recommended as follows: "Each single-dose vial delivers 0.9 mg inotuzumab ozogamicin, polysorbate 80 (xx mg), sodium chloride (xx mg), sucrose (xx mg), and tromethamine (xx mg)." *The Applicant revised as requested.* Revise the quantitative information (xx mg) in the inactive ingredients to that delivered in 3.6 mL. *The Applicant's revision is not acceptable. Product Quality team identified an incorrect calculation of the tromethamine amount* (b) (4) *mg) which should be revised to 8.64 mg.* *The Applicant revised as requested.*
Adjuvant, if present 21 CFR 610.61			x	
Source of the product 21 CFR 610.61			x	
Identity of each microorganism used in manufacturing 21 CFR 610.61			x	
Minimum potency of product 21 CFR 610.61		x		Per 21 CFR 610.61 (r), add the following statement to the side panel "No U.S. standard of potency". *The Applicant's revision is acceptable*

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Rx only 21 CFR 610.61	x			
Divided manufacturing 21 CFR 610.63			x	
Distributor 21 CFR 610.64			x	
Bar code 21 CFR 610.67 21 CFR 201.25	x			
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Preparation instructions 21 CFR 201.5		x		Revise the preparation instructions from (b) (4) to read "Reconstitute with 4 mL Sterile Water for Injection, USP to obtain a concentration of 0.25 mg/mL that delivers x mL (x mg). Gently swirl the vial to aid dissolution. Do Not Shake." *The Applicant revised* (b) (4) *The Applicant's revision is not acceptable. See Late Cycle Meeting minutes dated 23June17, Discussion section, and inactive ingredient comment to the applicant above.* *In the July 19, 2017 submission, the Applicant corrected the deliverable volume but expressed concern that the healthcare provider may assume the wrong concentration of the reconstituted solution.* Revise the reconstitution information as previously recommended, place it on a separate side panel from the inactive ingredient information, and increase the prominence of the recommended statement. You may consider removing the Proprietary name, proper name, dosage form, and strength from the side panel that contains the storage information, place it below the

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				storage information, and the use the bolded heading "Reconstitution:" as follows: "**Reconstitution:** Reconstitute with 4 mL Sterile Water for Injection, USP to obtain a concentration of 0.25 mg/mL that delivers 3.6 mL (0.9 mg). Gently swirl the vial to aid dissolution. Do Not Shake." *The Applicant revised as requested.*
Package type term 21 CFR 201.5	x			
Drugs Misleading statements 21 CFR 201.6	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			Revise the statement from [redacted] (b) (4) to read "See prescribing information for dosage, preparation, and administration." *The applicant's revision is acceptable*
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	

Prescribing Information Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)		x		Replace the following: [redacted] with the statement from the LRT: "See full prescribing information for instructions on reconstitution of lyophilized power, and preparation and administration of reconstituted drug (2.x)" *The Applicant accepted the revision*
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)		x		Revise from [redacted] to read ""For Injection: [redacted]mg [redacted]lyophilized [redacted]powder in a single-dose vial for reconstitution and further dilution." *The Applicant proposed to communicate that the concentration of the reconstituted solution (before further dilution) is 0.25 mg/mL, the Sponsor [redacted] See Late Cycle Meeting minutes dated 23June17 and Discussion section above.* Revise from [redacted] to read "For Injection: 0.9 mg lyophilized

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				powder in a single-dose vial for reconstitution and further dilution." *In the July 19, 2017 submission, the Applicant rejected the Agency's revision with the rationale to ensure appropriate dosing the applicant proposes to* (b) (4) We revised the strength to be consistent with the label claim and with the container and carton labeling. We are concerned that healthcare professionals (b) (4) stated in the labeling for one drug product resulting in prescribing and product preparation confusion. *The Applicant revised as requested.*
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)		x		Revise the second bullet under "Reconstitution" to read: "Reconstitute each (b) (4) vial with 4 mL of Sterile Water for Injection, USP to obtain a concentration of 0.25 mg/mL of BESPONSA that delivers (b) (4) mL (x mg)." *The Applicant proposed* (b) (4) *and revised the second bullet* (b) (4) *See Late Cycle Meeting minutes dated 23June17 and Discussion section above.* Revise the third bullet under "Reconstitution" to read: "Reconstitute each vial with 4 mL of Sterile Water for Injection, USP, to obtain a concentration of 0.25 mg/mL of BESPONSA that delivers 3.6 mL (0.9 mg). *The Applicant accepted this revision and also added*

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				the statement (b) (4) *This addition is unacceptable.* Delete the statement (b) (4) This information is not appropriate for the dosage and administration section of the labeling and is not required for this section per 21 CFR 201.57(c)(3). The strength should reflect the label claim and be consistent with the container and carton labeling. *The Applicant revised as requested.* Revise the second bullet under "Dilution" to read: "Add reconstituted solution to an infusion container (b) (4) 0.9% Sodium Chloride Injection, USP, to (b) (4) volume of 50 mL." *The Applicant accepted the revision.* Relocate the storage statement in bullets in the subsections for reconstitution, dilution, and administration to appear in Table 5 and replace with a bulleted statement to refer to Table 5 to reduce redundant information. *The Applicant accepted the revision.*
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Revise the sentence to read: For Injection: (b) (4) mg as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution. *The Applicant proposed to revise the statement to read* (b) (4) *mg as a white to off white lyophilized powder in a single-dose vial for reconstitution and further dilution.* (b) (4) *See Late Cycle Meeting minutes dated 23June17 and Discussion section above.*

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				Revise the sentence to read: "For Injection: 0.9 mg as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution." *The applicant rejected this revision and revise* (b) (4) Revise the sentence to read: "For Injection: 0.9 mg as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution." to be consistent with the label claim and with the container and carton labeling. *The Applicant revised as requested.*
6.2 IMMUNOGENICITY		x		Revise section 6.2 format to be consistent with the standard language for this section. *The Applicant revised as requested.*

11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Delete [redacted] from the first paragraph since the first paragraph describes the drug substance: "Inotuzumab ozogamicin is a CD22-directed antibody-drug conjugate…" *The Applicant accepted the revision.* In the second paragraph which describes the drug product, revise the dosage form to appear as "for Injection" and relocate the route of administration to appear after the characteristic description of the drug product: "BESPONSA (inotuzumab ozogamicin) for Injection is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous [redacted] " *The Applicant's revision is acceptable.* Revise so that the listing of the inactive ingredients appears in alphabetical order and the amounts are expressed in metric units: [redacted] polysorbate 80 ([redacted]mg), sodium chloride [redacted]mg), sucrose ([redacted]mg), and tromethamine ([redacted]mg) [redacted] After reconstitution with 4 mL of Sterile Water for Injection, USP, the final concentration is 0.25 mg/mL of inotuzumab ozogamicin with a deliverable volume of xx mL (x mg) and [redacted] pH [redacted] approximately 8.0." *The Applicant proposed to revise the paragraph to state [redacted] See Late Cycle Meeting minutes dated 23June17 and Discussion section above.* Revise the quantitative information (xx mg) in the inactive ingredients that is delivered in 3.6 mL. *The applicant revised as requested, however, PQ review team's calculations differ for tromethamine [redacted] vs. 8.64). Recalculate and if different explain your calculation.*

				The Applicant revised as requested.
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		Revise the sentences in section 16.1 to read: "BESPONSA (inotuzumab ozogamicin) for Injection is supplied [redacted] as a white to off-white lyophilized powder. Each carton (NDC 0008-0100-[redacted]) contains one single-dose vial." *The Applicant proposed to revise the paragraph to* [redacted] Revise the sentences in section 16.1 to read: "BESPONSA (inotuzumab ozogamicin) for Injection is supplied as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution. Each vial delivers 0.9 mg inotuzumab ozogamicin. Each carton (NDC 0008-0100-01) contains one single-dose vial." *The applicant accepted the revision.* Delete the sentences in section 16.2 to read: [redacted] per x21 CFR 201.57(c)(3) detailed storage conditions for reconstituted and diluted products should be described in the DOSAGE AND ADMINISTRATION section rather than the HOW SUPPLIED/STORAGE AND HANDLING section. *The applicant accepted the revision.*
Manufacturer information 21 CFR 610.61, 21 CFR 610.64				Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h (Pearl River, NY 10965) as follows: Applicant on Form FDA 356h Address US License No. xxxx - Remove [redacted] from the License No. statement.

				The applicant stated that the product is manufactured under US License Number 003, held by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc, with a registered address in Philadelphia, PA. The manufacturer's address on the label and carton is consistent with the biologics labeling regulations. The Sponsor will revise the 356h form to reflect the registered Philadelphia address for license number 003 so that it is consistent with the labeling. The "manufactured by" statement is consistent with the approved labeling for other biologic or vaccine products currently manufactured under license number 003. *The Applicant's revision is acceptable.*
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)			x	
Storage and Handling			x	
Ingredients			x	
Manufacturer Information 21 CFR 610.61, 21 CFR 610.64			x	

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

Vicky Borders-Hemphill

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Mate Tolnay

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Date: 8/08/2017 02:46:05PM
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First Approval for Indication
Breakthrough Designation w Priority Review
Orphan Drug

Recommendation: **Approval**

BLA Number: 761040
First Review
Review Date: June 28, 2017

Drug Name/Dosage Form	Besponsa (Inotuzumab Ozogamicin) / For injection
Strength/Potency	0.9 mg/vial, 0.25 mg/mL when diluted with 4 mL WFI
Route of Administration	Intravenous infusion after dilution
Rx/OTC Dispensed	Rx
Indication	Relapsed or refractory B-cell precursor ALL
Applicant/Sponsor	Pfizer, Inc.

Product Overview

BESPONSA (inotuzumab ozogamicin) is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl-gamma-calicheamicin that causes double-stranded DNA breaks, and 3) an acid-cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab. The average number of calicheamicin derivative molecules conjugated to each inotuzumab molecule is approximately 6 with a distribution from 2-8. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death. Besponsa is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous administration in a single-dose amber glass vial for reconstitution and further dilution. Each vial delivers 0.9 mg inotuzumab ozogamicin.

Quality Review Team

Discipline	Reviewer	Branch/Division
(b) (4) /Drug Substance Drug Product	Mate Tolnay	OBP/DBRR4
(b) (4) /Drug Substance Drug Product	Charles Jewell	ONDP/DNDAP1
CMC Labelling	Vicky Borders-Hemphill	OBP/IO
Facilities	Wayne Seifert	OPF/DIA
Microbiology	Maria Lopez-Barragan (DS) Natalia Pripuzova (DP)	OPF/DMA
Business RPM	Andrew Shiber	OPQ/OPRO
Team Lead ONDP	Benjamin Stevens	ONDP/DNDAP1
Team Lead Microbiology	Reyes Candau-Chacon	OPF/DMA
Team Lead Facilities	Peter Zhihao Qiu	OPF/DIA
Application Technical Lead	Gerald Feldman	OBP/DBRR4

Multidisciplinary Review Team

Discipline	Reviewer	Branch/Division
RPM	Rachel McMullen	OHOP/DHP
Cross-disciplinary Team Lead	R. Angelo De Claro	OHOP/DHP
Medical Officer	Tanya Wroblewski	OHOP/DHP
Pharm/Tox	Emily Place	OHOP/DHP
Clinical Pharmacology	Salaheldin Hamed	OHOP/DHP
Statistics	Qing Xu	OHOP/DHP

I. Names:

a. **Prorietary Name:** Besponsa™
b. **Trade Name:** Besponsa™
c. **Non-Proprietary/USAN:** inotuzumab ozogamicin
d. **CAS name:**
e. **Common Name:** Monoclonal anti-CD22 linked to calicheamicin
f. **INN Name:** inotuzumab ozogamicin
g. **OBP Systematic Name:** CONJ: MAB HUMANIZED (IGG4) ANTI P20273 (CD22_HUMAN); CALICHEAMICIN [CMC544]
h. **Other Names**: PF-05208773; CMC-544

a. Submissions Reviewed

Submission	Document Date
Original (rolling) submission (SD0001)	January 21, 2016
STN 761040/0002 Addition sections to submission	March 30, 2016
STN 761040/0003 Response to information request	April 1, 2016
STN 761040/0008 Response to information request	May 19, 2016
STN 761040/0009 Response to information request	May 24, 2016
STN 761040/0013 Updated stability data	May 31, 2016
STN 761040/0035 Response to information request	March 10, 2017
STN 761040/0042 Response to information request	April 3, 2017
STN 761040/0044 Response to information request	April 7, 2017
STN 761040/0048 Response to information request	April 25, 2017
STN 761040/0049 Response to information request	May 10, 2017
STN 761040/0052 Response to information request	May 24, 2017
STN 761040/0054 Response to information request	May 26, 2017
STN 761040/0056 Response to information request	June 13, 2017
STN 761040/0063 Response to information request	June 28, 2017

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related Supporting Documents:

A. DMFs

DMF #	DMF Holder	Item referenced	Code[1]	Status[2]	Review Completed	Comments
(b) (4)		(b) (4)	1	Adequate	5/15/2017	Reviewed by Charles Jewell
(b) (4)	Pfizer	(b) (4) Manufacturing Facility	1	Adequate	3/30/2017	Reviewed by Natalia Pripuzova
(b) (4)			2	Adequate	8/15/2016	Reviewed by Wendy Tang
			2	Adequate	8/25/2015	Reviewed by Lisa Shelton
			2	Adequate	10/1/2016	Reviewed by Wendy Tang
			3	Adequate	N/A	None

(b) (4)	3	Adequate	N/A	None

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other Documents: NONE

3. Consults Requested: NONE

APPEARS THIS WAY ON ORIGINAL

Executive Summary

I. Recommendations

a. Recommendation and Conclusion on Approvability

i. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends **Approval** of STN 761040 for **Besponsa** (inotuzumab ozogamicin) manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Besponsa is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

ii. Approval Action Letter Language

c. Manufacturing Location

(b) (4)

Drug Substance: Wyeth Pharmaceutical Division of Wyeth Holdings Corp., a subsidiary of Pfizer Inc., Pearl River, NY

Drug Product: Wyeth Pharmaceutical Division of Wyeth Holdings Corp., a subsidiary of Pfizer Inc., Pearl River, NY

d. Fill Size and Dosage Form

(b) (4) mg/vial lyophilized (b) (4) powder (b) (4): 0.25 mg/mL after reconstitution with 4 mL of sterile WFI

e. Dating Period

(b) (4)

Drug Substance: (b) (4) months when stored at (b) (4) °C.

Drug Product: 24 months when stored at 2-8°C

f. Stability

a. Results of on-going stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

g. Exempt from Lot Release

- Yes
- Rationale: Specified product exempted according to 21 CFR 601.2a)

b. Recommendation on Phase 4 Marketing Commitments, Agreements, and/or Risk Management Steps, if approvable: Product Quality (OPQ)

Office of Biotechnology Products: Not applicable

Office of Process and Facilities:

i. Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

ii. Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.

iii. Implement bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product.

c. Benefit/Risk Considerations: Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL), a disease which is considered an unmet medical need. Besponsa received breakthrough therapy designation on October 15, 2015, and was granted a priority review.

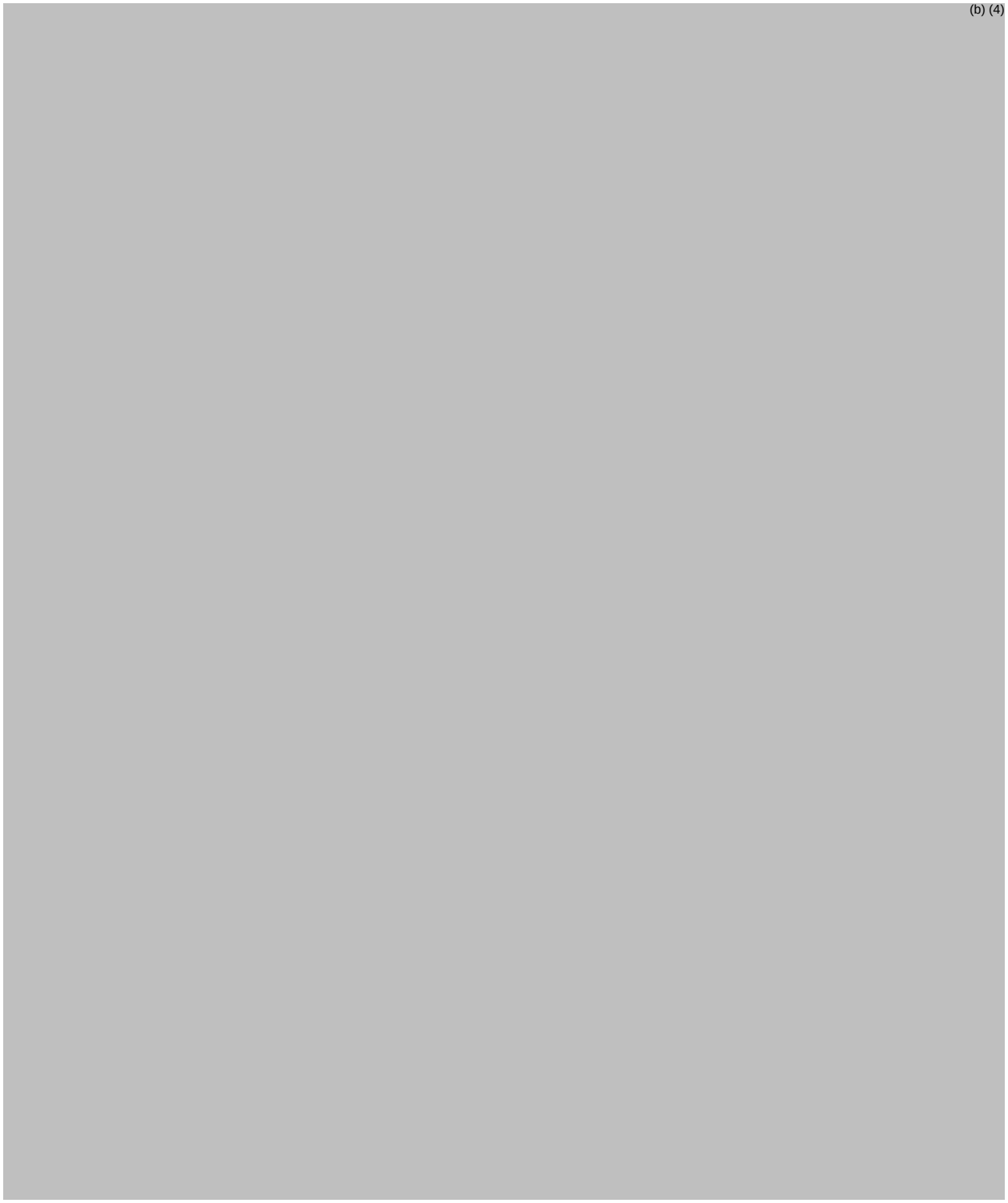
The overall control strategy for Besponsa includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. This control strategy combined with in-process, release, and stability testing ensure process consistency as well as (b) (4), drug substance, and drug product with appropriate quality attributes and free of adventitious agents.

II. Summary of Quality Assessments

(b) (4)

6 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



D. **Drug Substance Quality Assessment**

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for the drug substance CQAs that derive from the DS manufacturing process and general attributes. For additional information see Appendix A for the OBP product quality review.

Table 3: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Type	Risk	Origin	Control Strategy (b) (4)
Visual Appearance: color	General	Safety	Process failure; storage failure	
Appearance: clarity		Safety: Immunogenic response (with visible particles)		
Protein concentration		Efficacy	Process failure; CCI failure	
pH		Efficacy	Process failure; storage failure	
Total calichaemicin derivative		Safety and efficacy		
Drug-to-antibody ratio		Safety and efficacy		
Identity (conjugation profile / drug load distributions)		Safety and efficacy		
H+L chain	Purity	Impacts efficacy	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Intact IgG		Impacts efficacy	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Bioactivity (cell-based cytotoxicity assay)	Potency	Lower potency impacts efficacy, increased potency impacts safety	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Aggregates	Product-related Impurities	Safety and efficacy	Aggregates may form during all stages of the manufacturing process, as well as during storage.	
Unconjugated calicheamicin		Safety	Originate in the manufacturing process. (b) (4)	

			(b) (4)	(b) (4)
Unconjugated mAb		Efficacy		
Bioburden		Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	
Endotoxin		Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	

iv. Drug Substance (inotuzumab ozogamicin) Quality Summary

1. **Description**: Inotuzumab ozogamicin is an antibody drug conjugate comprised of multiple (2-8) molecules of calicheamicin bound per molecule of inotuzumab, with a molecular weight of approximately 160 kDa.
2. **Mechanism of action**: The primary mechanism of action of inotuzumab ozogamicin is tumor cell killing thought to be due to its binding to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of the cytotoxic calicheamicin moiety.
3. **Potency Assay**: The potency assay used to assess the biological activity of inotuzumab ozogamicin for release and stability is a Ramos cell-based cytotoxicity assay. Results are reported as percent potency relative to the reference standard.

4. **Reference material(s)**: A two tiered reference standard system is in place. (b) (4)

5. **Critical starting materials or intermediates**: (b) (4)

6. **Container closure**: (b) (4)

7. **Dating period and storage conditions**: The stability data provided for the DS in the BLA support an expiry of (b) (4) months when stored at (b) (4) °C ± (b) (4) °C.

E. **Drug Product [Besponsa] Quality Assessment**

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information see Appendix A for the OBP product quality review.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA	Type	Risk	Origin	Control Strategy	Notes
Appearance (b) (4)	General	Safety: Immunogenic response (with visible particles)	Process failure; Inappropriate storage	(b) (4)	
Appearance (reconstituted)					
Osmolality		Safety (site reaction)			

Moisture Content		Product stability	Process failure; Inappropriate storage; CCI failure	(b) (4)	
Reconstitution Time					
PS80 concentration	Formulation component	(b) (4)	Manufacturing process failure		
PS80 quality			Quality of raw material (b) (4) and storage		
Particulates	Product and process related impurity	Safety. Product stability	Manufacturing process failure; Inappropriate storage		
Container Closure System Integrity	Safety and efficacy	Maintenance of sterility. Glass (b) (4) Leachables from the stopper	Quality of raw materials; System integrity for sterility impacted by storage conditions		
Sterility		Safety risk to patients (infection). Efficacy (degradation or modification of the product by microorganisms or their byproducts)	DP manufacturing process or through container closure integrity failure		
Endotoxins	Safety	Safety, purity and potential immunogenic reactions	Introduced through DP manufacturing process		

v. Drug Product (inotuzumab ozogamicin) Quality Summary

1. **Potency and Strength**: Besponsa is supplied as a single-use (b) (4) mg/vial lyophilate (0.9 mg (b) (4).
2. **Description/Commercial Image**: Besponsa (inotuzumab ozogamacin) is a sterile, white to off-white, preservative-free, lyophilized powder for intravenous administration. After reconstitution with 4 mL of Sterile Water for Injection, USP, the final concentration is 0.25 mg/mL of inotuzumab ozogamicin with (b) (4)
3. **Mechanism of action**: The primary mechanism of action of inotuzumab ozogamicin is tumor cell killing thought to be due to its binding to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of the cytotoxic calicheamicin moiety.
4. **List of Excipients**: tromethamine (b) (4), sucrose (b) (4), polysorbate 80 (b) (4), NaCl (b) (4)
5. **Reference material(s)**: (b) (4)
6. **Container closure**: Inotuzumab ozogamicin drug product is packaged in 20 mL amber Type I glass tubing vials with (b) (4) stoppers and crimp seals with flip-off caps. Validation studies (including leachable and extractable studies) were conducted on these components to demonstrate that they are suitable for use. Besponsa is diluted with 4 mL of sterile water for injection to a concentration of 0.25 mg/mL and further diluted with 0.9% sterile normal saline prior to administration by intravenous infusion. The maximum validated time from reconstitution to administration is 8 hours.
7. **Dating period and storage conditions**: The stability data provided for the DP in the BLA support an expiry of 24 months when stored at 2-8°C.
8. **List of co-packaged components:** Not applicable

F. **Novel Approaches/Precedents:** None

G. **Special Product Quality Labeling Recommendations:**
   1. Store in a refrigerator at 2-8°C
   2. Protect from light during reconstitution, dilution, and administration
   3. Do not freeze
   4. Do not shake
   5. Use reconstituted material immediately, or store refrigerate (2-8°C) for up to 4 hours.
   6. Use diluted material immediately, or store at room temperature (20-25°C; 68-77°F) for up to 4 hours or refrigerated (2-8°C; 36-46°F) for up to 3 hours.
   7. If refrigerated, allow to equilibrate at room temperature (20-25°C; 68-77°F) for 1 hour prior to administration

H. **Establishment Information:**

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Master and working cell bank storage Working Cell Bank Preparation and Cell Bank storage.	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland And Pfizer Inc. 700 Chesterfield Parkway West Chesterfield, MO 63017 USA And Wyeth BioPharma One Burtt Road Andover, MA 01810 USA	3004145594 1940118 1222181	VAI	None	Recommend for approval
(b) (4)			VAI	None	Recommend for approval
Manufacture of DS Release and stability testing, storage	Wyeth Pharmaceutical 401 North Middletown Road, Pearl River, New York 10965 USA	2410662	VAI	None	Recommend for approval
(b) (4)			VAI	None	Recommend for approval

(b) (4)				
In-process testing	(b) (4)	VAI	None	Recommend for approval
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Manufacture of drug product, release testing, stability testing, storage	Wyeth Pharmaceutical 401 North Middletown Road, Pearl River, New York 10965 USA	2410662	VAI	None	Recommend for approval
Drug product secondary packaging and labeling	Pharmacia and Upjohn Co 7000 Portage Road Kalamazoo, Michigan 49001	1810189	VAI	None	Recommend for approval
Drug product stability testing (CCI)	(b) (4)		VAI	None	Recommend for approval

I. **Facilities:**

(b) (4)

A pre-license inspection of the inotuzumab ozogamicin Drug Substance and Drug Product manufacturing facility at Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Pearl River, NY, was conducted on March 9 - 17, 2017.

The compliance status of this manufacturing site was deemed acceptable.

For additional information, see Appendices C and D for the DMA reviews and Appendix E for the DIA review.

J. Lifecycle Knowledge Management

(b) (4)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Substance

i. Protocols approved:

1. Annual stability protocols
2. Protocols for the qualification of (b) (4) reference standards
3. Protocols for (b) (4)

ii. Outstanding review issues/residual risk:

1. Data for the full qualification of bioburden and endotoxin test methods will be submitted by November, 2017

iii. Future inspection points to consider: None

c. Drug Product

i. Protocols approved:

1. Annual stability protocols

ii. Outstanding review issues/residual risk:

1. Data for the full qualification of sterility and endotoxin test methods will be submitted by November, 2017
2. Implementation of bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product will be finalized by November, 2017

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug			
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other: Antibody-drug conjugate	X		
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		X	
16.	Comparability Protocol(s)		X	

17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____			X	
Quality Considerations					
21.	Drug Substance Overage				
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)		X		
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	

38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other _____		X	

Appendices:

Appendix A; Link to CMC Review

Appendix B; Link to ONDP Review

Appendix C; Link to DMA DS Review

Appendix D; Link to DMA DP Review

Appendix E; Link to DIA Review

Quality Review Team – Signature Page

Reviewer	Division	Signature
Mate Tolnay	Division of Biotechnology Review and Research IV	Electronic Signatures Attached
Maria Lopez-Barragan	Division of Microbiology Assessment	
Natalia Pripuzova	Division of Microbiology Assessment	
Charles Jewell	Division of New Drug Products I	
Wayne Seifert	Division of Inspectional Assessment	
Benjamin Stevens	Division of New Drug Products I	
Maria Reyes Candau-Chacon	Division of Microbiology Assessment	
Peter Zhihao Qiu	Division of Inspectional Assessment	
Gerald Feldman	Division of Biotechnology Review and Research IV	
Joel Welch	Division of Biotechnology Review and Research IV	

Gerald Feldman

Digitally signed by Gerald Feldman
Date: 7/03/2017 11:56:55AM
GUID: 508da6d7000262b8e01063de903db2bf

Mate Tolnay

Digitally signed by Mate Tolnay
Date: 7/03/2017 12:04:56PM
GUID: 508da6d8000263782a9fcccefaa2c6f0

Charles Jewell

Digitally signed by Charles Jewell
Date: 7/03/2017 12:04:38PM
GUID: 504e331900000700b896c504b8c57bb3

Maria Jose Lopez-Barragan

Digitally signed by Maria Jose Lopez-Barragan
Date: 7/05/2017 10:14:33AM
GUID: 5565e91d00144667b9fe95c7f98fbf85

Wayne Seifert

Digitally signed by Wayne Seifert
Date: 7/03/2017 04:27:33PM
GUID: 54947cf700352f7777a77d75519a2705

Ben Stevens

Digitally signed by Ben Stevens
Date: 7/03/2017 11:56:10AM
GUID: 5432b4d800086115752a874a47534532

Patricia Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 7/03/2017 11:57:04AM
GUID: 508da717000297bcbfce0919f8c09594

Joel Welch

Digitally signed by Joel Welch
Date: 7/03/2017 02:32:27PM
GUID: 508da6dc0002673d83d264d81364d6cf

Thuy Thanh Nguyen

Digitally signed by Thuy Thanh Nguyen
Date: 7/03/2017 01:11:33PM
GUID: 5256cce70002b21dd4c17f3ef09b075c

First Approval for Indication
Breakthrough Designation w Priority Review
Orphan Drug

Recommendation: **Approval**

BLA Number: 761040
First Review
Review Date: June 28, 2017

Drug Name/Dosage Form	Besponsa (Inotuzumab Ozogamicin) / For injection
Strength/Potency	0.9 mg/vial, 0.25 mg/mL when diluted with 4 mL WFI
Route of Administration	Intravenous infusion after dilution
Rx/OTC Dispensed	Rx
Indication	Relapsed or refractory B-cell precursor ALL
Applicant/Sponsor	Pfizer, Inc.

Product Overview

BESPONSA (inotuzumab ozogamicin) is a CD22-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the recombinant humanized immunoglobulin class G subtype 4 (IgG4) kappa antibody inotuzumab, specific for human CD22, 2) N-acetyl-gamma-calicheamicin that causes double-stranded DNA breaks, and 3) an acid-cleavable linker composed of the condensation product of 4-(4'-acetylphenoxy)-butanoic acid (AcBut) and 3-methyl-3-mercaptobutane hydrazide (known as dimethylhydrazide) that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab. The average number of calicheamicin derivative molecules conjugated to each inotuzumab molecule is approximately 6 with a distribution from 2-8. Nonclinical data suggest that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of N-acetyl-gamma-calicheamicin dimethylhydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl-gamma-calicheamicin dimethylhydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death. Besponsa is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous administration in a single-dose amber glass vial for reconstitution and further dilution. Each vial delivers 0.9 mg inotuzumab ozogamicin.

Quality Review Team

Discipline	Reviewer	Branch/Division
(b) (4)/Drug Substance Drug Product	Mate Tolnay	OBP/DBRR4
(b) (4)/Drug Substance Drug Product	Charles Jewell	ONDP/DNDAP1
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Multidisciplinary Review Team

Discipline	Reviewer	Branch/Division
RPM	Rachel McMullen	OHOP/DHP
Cross-disciplinary Team Lead	R. Angelo De Claro	OHOP/DHP
Medical Officer	Tanya Wroblewski	OHOP/DHP
Pharm/Tox	Emily Place	OHOP/DHP
Clinical Pharmacology	Salaheldin Hamed	OHOP/DHP
Statistics	Qing Xu	OHOP/DHP

I. Names:

a. **Prorietary Name:** Besponsa™
b. **Trade Name:** Besponsa™
c. **Non-Proprietary/USAN:** inotuzumab ozogamicin
d. **CAS name:**
e. **Common Name:** Monoclonal anti-CD22 linked to calicheamicin
f. **INN Name:** inotuzumab ozogamicin
g. **OBP Systematic Name:** CONJ: MAB HUMANIZED (IGG4) ANTI P20273 (CD22_HUMAN); CALICHEAMICIN [CMC544]
h. **Other Names**: PF-05208773; CMC-544

a. Submissions Reviewed

Submission	Document Date
Original (rolling) submission (SD0001)	January 21, 2016
STN 761040/0002 Addition sections to submission	March 30, 2016
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STN 761040/0052 Response to information request	May 24, 2017
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STN 761040/0056 Response to information request	June 13, 2017
STN 761040/0063 Response to information request	June 28, 2017

Quality Review Data Sheet

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A. DMFs

DMF #	DMF Holder	Item referenced	Code[1]	Status[2]	Review Completed	Comments
(b) (4)		(b) (4)	1	Adequate	5/15/2017	Reviewed by Charles Jewell
(b) (4)		(b) (4)	1	Adequate	3/30/2017	Reviewed by Natalia Pripuzova
(b) (4)			2	Adequate	8/15/2016	Reviewed by Wendy Tang
			2	Adequate	8/25/2015	Reviewed by Lisa Shelton
			2	Adequate	10/1/2016	Reviewed by Wendy Tang
			3	Adequate	N/A	None

(b) (4)	3	Adequate	N/A	None

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other Documents: NONE

3. Consults Requested: NONE

Quality Review Team – Signature Page

Reviewer	Division	Signature
Mate Tolnay	**Division of Biotechnology Review and Research IV**	**Electronic Signatures Attached**
Maria Lopez-Barragan	**Division of Microbiology Assessment**	
Natalia Pripuzova	**Division of Microbiology Assessment**	
Charles Jewell	**Division of New Drug Products I**	
Wayne Seifert	**Division of Inspectional Assessment**	
Benjamin Stevens	**Division of New Drug Products I**	
Maria Reyes Candau-Chacon	**Division of Microbiology Assessment**	
Peter Zhihao Qiu	**Division of Inspectional Assessment**	
Gerald Feldman	**Division of Biotechnology Review and Research IV**	
Joel Welch	**Division of Biotechnology Review and Research IV**	

Executive Summary

I. Recommendations

a. Recommendation and Conclusion on Approvability

i. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends **Approval** of STN 761040 for **Besponsa** (inotuzumab ozogamicin) manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Besponsa is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

ii. Approval Action Letter Language

c. Manufacturing Location

(b) (4)

Drug Substance: Wyeth Pharmaceutical Division of Wyeth Holdings Corp., a subsidiary of Pfizer Inc., Pearl River, NY

Drug Product: Wyeth Pharmaceutical Division of Wyeth Holdings Corp., a subsidiary of Pfizer Inc., Pearl River, NY

d. Fill Size and Dosage Form

(b) (4) mg/vial lyophilized (b) (4) powder (b) (4): 0.25 mg/mL after reconstitution with 4 mL of sterile WFI

e. Dating Period

(b) (4)

Drug Substance: (b) (4) months when stored at (b) (4) °C.

Drug Product: 24 months when stored at 2-8°C

f. Stability

a. Results of on-going stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

g. Exempt from Lot Release

- Yes
- Rationale: Specified product exempted according to 21 CFR 601.2a)

b. Recommendation on Phase 4 Marketing Commitments, Agreements, and/or Risk Management Steps, if approvable: Product Quality (OPQ)

Office of Biotechnology Products: Not applicable

Office of Process and Facilities:

i. Conduct the bioburden and endotoxin test method qualification of inotuzumab ozogamicin drug substance using two additional batches.

ii. Conduct the sterility and endotoxin test method qualification of inotuzumab ozogamicin drug product using two additional batches.
iii. Implement bioburden and endotoxin monitoring of the (b) (4) (b) (4) used to manufacture inotuzumab ozogamicin drug product.

c. Benefit/Risk Considerations: Besponsa is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22 positive B cell precursor acute lymphoblastic leukaemia (ALL), a disease which is considered an unmet medical need. Besponsa received breakthrough therapy designation on October 15, 2015, and was granted a priority review.

The overall control strategy for Besponsa includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. This control strategy combined with in-process, release, and stability testing ensure process consistency as well as (b) (4) drug substance, and

(b) (4)

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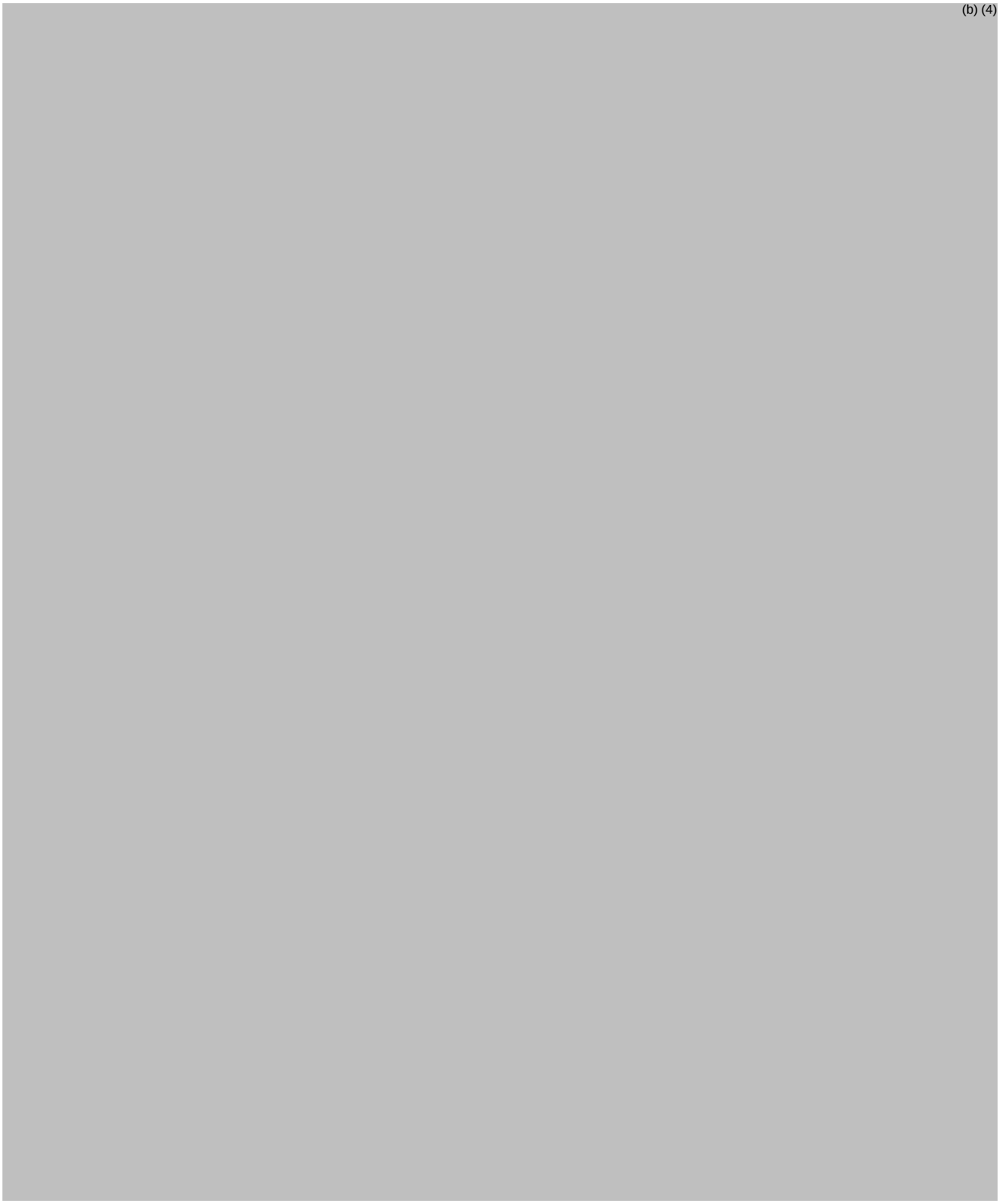
(b) (4)



D

management for the drug substance CQAs that derive from the DS manufacturing process and general attributes. For additional information see Appendix A for the OBP product quality review.

Table 3: Drug Substance CQA Identification, Risk, and Lifecycle Knowle

CQA (Type)	Type	Risk	Origin	
Visual Appearance: color	General	Safety	Process failure; storage failure	(b) (4)
Appearance: clarity		Safety: Immunogenic response (with visible particles)		
Protein concentration		Efficacy	Process failure; CCI failure	
pH		Efficacy	Process failure; storage failure	
Total calichaemicin derivative		Safety and efficacy		
Drug-to-antibody ratio		Safety and efficacy		
Identity (conjugation profile / drug load distributions)		Safety and efficacy		
H+L chain	Purity	Impacts efficacy	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Intact IgG		Impacts efficacy	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Bioactivity (cell-based cytotoxicity assay)	Potency	Lower potency impacts efficacy, increased potency impacts safety	Structure may be impacted during all stages of the manufacturing process, as well as during storage	
Aggregates	Product-related Impurities	Safety and efficacy	Aggregates may form during all stages of the manufacturing process, as well as during storage.	
Unconjugated calicheamicin		Safety	Originate in the manufacturing process. (b) (4)	(b) (4)

			(b) (4)	(b) (4)
Unconjugated mAb		Efficacy		
Bioburden		Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process	
Endotoxin		Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	

iv. Drug Substance (inotuzumab ozogamicin) Quality Summa

1. **Description**: Inotuzumab ozogamicin is an antibody drug comprised of multiple (2-8) molecules of calicheamicin bound per molecule of inotuzumab, with a molecular weight of approximately 160 kDa.
2. **Mechanism of action**: The primary mechanism of action of inotuzumab ozogamicin is tumor cell killing thought to be due to its binding to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of the cytotoxic calicheamicin moiety.
3. **Potency Assay**: The potency assay used to assess the biological activity of inotuzumab ozogamicin for release and stability is a Ramos cell-based cytotoxicity assay. Results are reported as percent potency relative to the reference standard.

4. [redacted]

5. [redacted]

6. **C** [redacted]

7. **Dating period and storage conditions**: The stability data provided for the DS in the BLA support an expiry of [redacted] months when stored at [redacted] °C ± [redacted] °C.

E. **Drug Product [Besponsa] Quality Assessment**

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information see Appendix A for the OBP product quality review.

Table 4: Drug Product CQA Identification, Risk, and Lifecy ement

CQA	Type	Risk	Origin	[redacted]	Notes
Appearance [redacted]	General	Safety: Immunogenic response (with visible particles)	Process failure; Inappropriate storage	[redacted]	
Appearance (reconstituted)					
Osmolality		Safety (site reaction)			

Moisture Content			Process failure; Inappropriate storage; CCI failure	(b) (4)
Reconstitution Time				
PS80 concentration	Formulation component	(b) (4)	Manufacturing process failure	
PS80 quality			Quality of raw material (b) (4) (b) (4) and storage	
Particulates	Product and process related impurity	stability	Manufacturing process failure; Inappropriate storage	
Container Closure System Integrity	Safety and efficacy	Maintenance of sterility. Glass (b) (4) Leachables from the stopper	Quality of raw materials; System integrity for sterility impacted by storage conditions	
Sterility		Safety risk to patients (infection). Efficacy (degradation or modification of the product by microorganisms or their byproducts)	DP manufacturing process or through container closure integrity failure	
Endotoxins	Safety	Safety, purity and potential immunogenic reactions	Introduced through DP manufacturing process	

v. Drug Product (inotuzumab ozogamicin) Quality

1. **Potency and Strength**: Besponsa is supplied as a single-use (b) (4) mg/vial lyophilate (0.9 mg (b) (4)
2. **Description/Commercial Image**: Besponsa (inotuzumab ozogamacin) is a sterile, white to off-white, preservative-free, lyophilized powder for intravenous administration. After reconstitution with 4 mL of Sterile Water for Injection, USP, the final concentration is 0.25 mg/mL of inotuzumab ozogamicin with (b) (4) (b) (4)
3. **Mechanism of action**: The primary mechanism of action of inotuzumab ozogamicin is tumor cell killing thought to be due to its binding to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of the cytotoxic calicheamicin moiety.
4. **List of Excipients**: tromethamine (b) (4), sucrose (b) (4) polysorbate 80 (b) (4), NaCl (b) (4)
5. **Reference material(s)**: (b) (4) (b) (4)
6. **Container closure**: Inotuzumab ozogamicin drug product is packaged in 20 mL amber Type I glass tubing vials with (b) (4) stoppers and crimp seals with flip-off caps. Validation studies (including leachable and extractable studies) were conducted on these components to demonstrate that they are suitable for use. Besponsa is diluted with 4 mL of sterile water for injection to a concentration of 0.25 mg/mL and further diluted with 0.9% sterile normal saline prior to administration by intravenous infusion. The maximum validated time from reconstitution to administration is 8 hours.
7. **Dating period and storage conditions**: The stability data provided for the DP in the BLA support an expiry of 24 months when stored at 2-8°C.
8. **List of co-packaged components:** Not applicable

F. **Novel Approaches/Precedents:** None

G. **Special Product Quality Labeling Recommendations:**

1. Store in a refrigerator at 2-8°C
2. Protect from light during reconstitution, dilution, and administration
3. Do not freeze
4. Do not shake
5. Use reconstituted material immediately, or store refrigerate (2-8°C) for up to 4 hours.
6. Use diluted material immediately, or store at room temperature (20-25°C; 68-77°F) for up to 4 hours or refrigerated (2-8°C; 36-46°F) for up to 3 hours.
7. If refrigerated, allow to equilibrate at room temperature (20-25°C; 68-77°F) for 1 hour prior to administration

H. Establishment Information:

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Master and working cell bank storage Working Cell Bank	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland And Pfizer Inc. 700 Chesterfield Parkway West Chesterfield, MO 63017 USA And Wyeth	3004145594 1940118 1222181	VAI	None	Recommend for approval
(b) (4)			VAI	None	Recommend for approval
stability testing, storage	Middletown Road, Pearl River, New York 10965 USA	2410662	VAI	None	Recommend for approval
(b) (4)			VAI	None	Recommend for approval

[redacted] (b) (4)				
	[redacted] (b) (4)	VAI	None	Recommend for approval

DRUG PRODUCT

FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Manufacture of drug product, release testing, stability testing, storage	Wyeth Pharmaceutical 401 North Middletown Road, Pearl River, New York 10965 USA	2410662	VAI	None	Recommend for approval
Drug product secondary packaging and labeling	Pharmacia and Upjohn Co 7000 Portage	9	VAI	None	Recommend for approval
Drug product stability testing (CCI)	[redacted] (b) (4)		VAI	None	Recommend for approval

I. **F**

[redacted] (b) (4)

er

Inc., Pearl River, NY, was conducted on March 9 - 17, 2017.

The compliance status of this manufacturing site was deemed acceptable.

For additional information, see Appendices C and D for the DMA reviews and A

J. **Lifec**

(b) (4)

i. Protocols approved:

1. Annual stability protocols
2. Protocols for the qualification of (b) (4) (b) (4) reference standards
3. Protocols for (b) (4)

ii. Outstanding review issues/residual risk:

1. Data for the full qualification of bioburden and endotoxin test methods will be submitted by November, 2017

iii. Future inspection points to consider: None

c. Drug Product

i. Protocols approved:

1. Annual stability protocols

ii. Outstanding review issues/residual risk:

1. Data for the full qualification of sterility and endotoxin test methods will be submitted by November, 2017
2. Implementation of bioburden and endotoxin monitoring of the (b) (4) used to manufacture inotuzumab ozogamicin drug product will be finalized by November, 2017

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug			
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other: Antibody-drug conjugate	X		
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		X	
16.	Comparability Protocol(s)		X	

17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____			X	
Quality Considerations					
21.	Drug Substance Overage				
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)		X		
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	

38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other _____		X	

APPEARS THIS WAY ON ORIGINAL

Mate Tolnay

Digitally signed by Mate Tolnay
Date: 7/03/2017 12:07:02PM
GUID: 508da6d8000263782a9fcccefaa2c6f0

Maria Jose Lopez-Barragan

Digitally signed by Maria Jose Lopez-Barragan
Date: 7/05/2017 10:14:19AM
GUID: 5565e91d00144667b9fe95c7f98fbf85

Charles Jewell

Digitally signed by Charles Jewell
Date: 7/03/2017 12:03:16PM
GUID: 504e331900000700b896c504b8c57bb3

Wayne Seifert

Digitally signed by Wayne Seifert
Date: 7/04/2017 01:27:46AM
GUID: 54947cf700352f7777a77d75519a2705

Ben Stevens

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Patricia Hughes Troost

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Joel Welch

Digitally signed by Joel Welch
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GUID: 508da6dc0002673d83d264d81364d6cf

Gerald Feldman

Digitally signed by Gerald Feldman
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Thuy Thanh Nguyen

Digitally signed by Thuy Thanh Nguyen
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BLA STN 761040

Inotuzumab Ozogamicin

Pfizer

Mate Tolnay, Primary Reviewer
Gerald Feldman, Application Team Lead
Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. **BLA: STN 761040**

2. **FINAL REVIEW DATE: June 28, 2017**

3. **PRIMARY REVIEW TEAM:**

Medical Officer:	Tanya Wroblewski
Pharm/Tox:	Emily Place
Product Quality Team:	Mate Tolnay
Small Drug Reviewer:	Charles Jewell
BMT / Facilities:	Maria Jose Lopez-Barragan/ Wayne Seifert
Clinical Pharmacology:	Salaheldin Hamed/ Bahru Habtemariam
Statistics:	Qing Xu
OBP Labeling:	Vicky Borders-Hemphill
RPM:	Rachel McMullen

4. **MAJOR GRMP DEADLINES**

Filing Meeting:	**January 12, 2017**
Mid-Cycle Meeting:	**March 21, 2017**
Wrap-Up Meeting:	**July 27, 2017**
Primary Review Due:	**May 20, 2017**
Secondary Review Due:	**May 30, 2017**
CDTL Memo Due:	**July 10, 2017**
PDUFA Action Date:	**August 20, 2017**

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information request #1	May 10, 2016
Information request #2	March 1, 2017
Teleconference	May 3, 2017
Information request #3	May 9, 2017
Information request #4	June 6, 2017
Information request #5	June 26, 2017

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
Original submission with CMC (SD1)	January 21, 2016	Yes
Submission with additional sections (SD2)	March 30, 2016	Yes
Response to information request #1 (SD9)	May 24, 2016	Yes
Updated stability data (SD13)	May 31, 2016	Yes
Response to information request #2 (SD44)	April 7, 2017	Yes

Response to information request #3 (SD52)	May 24, 2017	Yes
Response to teleconference request (SD54)	May 26, 2017	Yes
Response to information request #4 (SD56)	June 13, 2017	Yes
Response to information request #5 (SD63)	June 28, 2017	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Besponsa
   b. Trade Name: Besponsa
   c. Non-Proprietary/USAN: Inotuzumab Ozogamicin
   d. CAS name:
   e. Common name: Monoclonal anti-CD22 linked to calicheamicin
   f. INN Name: Inotuzumab Ozogamicin
   g. Compendial Name:
   h. OBP systematic name: CONJ: MAB HUMANIZED (IGG4) ANTI P20273 (CD22_HUMAN); CALICHEAMICIN [CMC544]
   i. Other Names: PF-05208773; CMC-544

8. **PHARMACOLOGICAL CATEGORY:** Antibody drug conjugate
9. **DOSAGE FORM:** Lyophilized
10. **STRENGTH/POTENCY:**
    (i) The strength of Besponsa Drug Product is (b) (4) mg lyophilized protein to be reconstituted in 4 ml volume (0.9 mg (b) (4)
    (ii) The potency assay is a cell killing bioassay. CD22-expressing Ramos cells are incubated with serially diluted inotuzumab ozogamicin for four days. At the end of the incubation period, a luminescent cell viability reagent is utilized to detect the level of ATP. The potency specification is 74%-126% potency relative to the reference standard.
11. **ROUTE OF ADMINISTRATION:** Intravenous
12. **REFERENCED MASTER FILES:**

			Letter of Cross-Reference	**COMMENTS (STATUS)**
(b) (4)				Reviewed by Charles Jewell.
			Yes	Reviewed by Mate Tolnay
			Yes	Reviewed by Mate Tolnay

A pre-license inspection of the (b) (4) (b) (4) (b) (4) was conducted on (b) (4) by Wayne Seifert and Mate Tolnay. The inspection covered the manufacturing of (b) (4) A one-item Form FDA 483 was issued. A pre-license inspection of the inotuzumab ozogamicin Drug Substance and Drug Product manufacturing facility at Wyeth

Pharmaceuticals Inc., a subsidiary of Pfizer Inc., Pearl River, NY, was conducted on March 9 - 17, 2017 by Maria Jose Lopez Barragan, Diane Raccasi, Wayne Seifert, Marjorie Shapiro, Mate Tolnay, Antonina Aydanian and Charles Jewell. This pre-license inspection was conducted in support of two BLA; Mylotarg (BLA 761060) and Besponsa (BLA 761040). A seven item Form FDA 483 was issued.

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS:

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS: None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Review Chief (acting), Division of Biotechnology Review and Research IV	
Gerald M. Feldman, Ph.D. Application Team Leader, Division of Biotechnology Review and Research IV	
Mate Tolnay, Ph.D. CMC Reviewer, Division of Biotechnology Review and Research IV	

B. CC Block

Recipient	Date
Clinical Division BLA RPM	

Division of Biotechnology Review and Research IV File/BLA STN 761040	

APPEARS THIS WAY ON ORIGINAL

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Besponsa (inotuzumab ozogamicin) is well controlled, and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured form multiple production runs. It is recommended that Besponsa (inotuzumab ozogamicin) be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) (b) (4)

We recommend an expiration dating period of (b) (4) months for inotuzumab ozogamicin drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 24 months for inotuzumab ozogamicin drug product when stored at 2-8°C.

We recommend approval of the proposed release and shelf-life test methods and specifications for (b) (4) inotuzumab ozogamicin drug substance and drug product.

II. List of Deficiencies To Be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments/Requirement

IV. Review of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). ***The claim of categorical exemption is accepted.***

V. Primary Container Labeling Review

The CMC review of the Drug Product Label was performed by Vicky Borders-Hemphill and Mate Tolnay.

VI. Review of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The primary immunogenicity assay has sufficient sensitivity (215 ng/mL) and it has acceptable drug tolerance (2.76 µg/ml of anti-inotuzumab can be determined to be positive in a sample containing up to 5 µg/mL drug), considering the maximum drug serum concentration in patients. The primary immunogenicity assay is adequately validated.

The cell-based neutralizing antibody assay has sufficient sensitivity (58.3 ng/mL) and it has acceptable drug tolerance (1 µg/mL drug). The neutralizing antibody assay is adequately validated.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT
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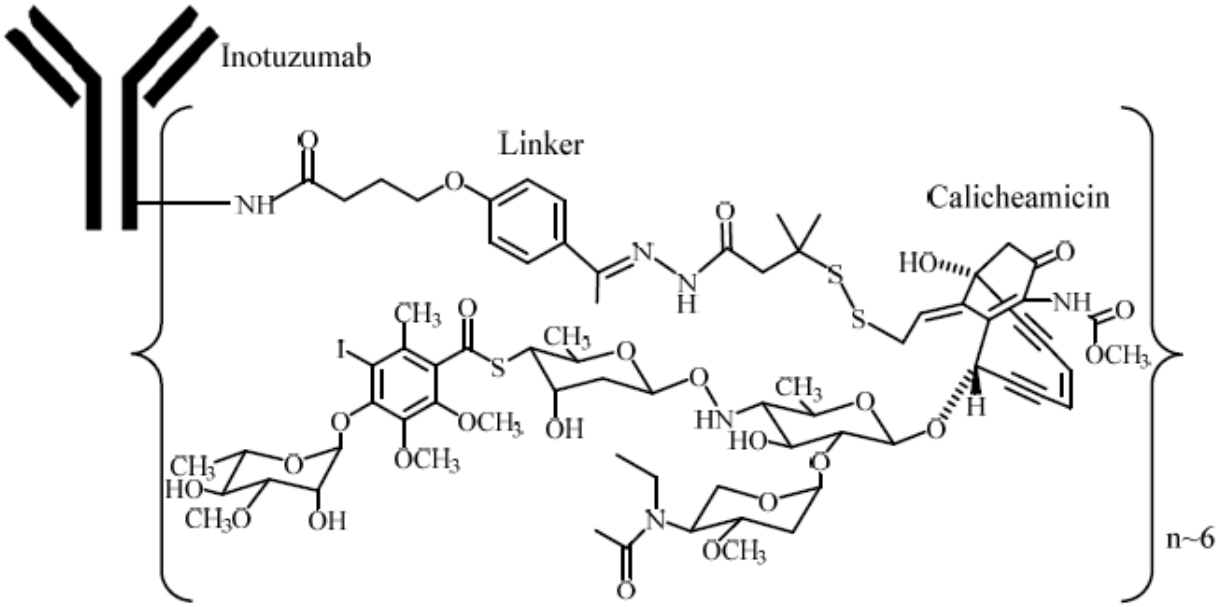
INOTUZUMAB OZOGAMICIN

3.2.S.1.2 Structure

The average number of calicheamicin derivatives conjugated to each inotuzumab molecule is ~6 with a distribution from 2 to 8. An inotuzumab ozogamicin molecule with G0F/G0F glycoform and 6 calicheamicins has a theoretical molecular mass of 159,256 Da.



3.2.S.1.3 General Properties

Inotuzumab ozogamicin consists of a humanized IgG4 mAb (inotuzumab; G544) covalently linked to a semi-synthetic derivative of calicheamicin (PF-06301660). Inotuzumab targets CD22 expressed on B cells. Calicheamicin is bound to the mAb via a linker, which forms an amide bond with the mAb and a disulfide bond with the calicheamicin. The linker also contains an internal acid-labile hydrazone bond. Upon binding to its target, the conjugate is internalized by endocytosis. Hydrolysis of the linker can occur in the acidic environment of lysosomes. Following hydrolytic cleavage of the linker, calicheamicin binds to the DNA minor groove, resulting in cell death by inducing double strand DNA breaks. The linker was designed to achieve a balance between release in the tumor cell and stability in circulation.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The DS is manufactured and tested by Wyeth Pharmaceutical, a subsidiary of Pfizer, 401 North

(b) (4)

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3.2.P.7 Container Closure System

The DP is packaged in amber Type I glass tubing vials with (b) (4) stoppers and crimp seals with flip-off caps. Validation studies were conducted on these components to demonstrate that they are suitable for use (Section 3.2.P.2.4 Container Closure System).

The glass vial consists of amber Type I (b) (4) glass and has a 20 mL nominal fill volume. The vial meets USP <660>, Ph. Eur. 3.2.1, and JP 7.01 requirements for amber Type I glass containers. The stopper is a 20 mm lyophilization design constructed (b) (4) (b) (4) The stopper meets the requirements of the USP <381>, Ph. Eur. 3.2.9 and JP 7.03. The seal is a 20 mm aluminum design with a flip-off cap.

The carton used for secondary packaging is constructed of cardboard. Each carton consists of the labeled drug product vial and the package insert or instructions for use.

Reviewer comment*: The dimension limits of the vial, stopper and seal were provided. Vials are made by* (b) (4) *stoppers are made by* (b) (4) *the seal is made by* (b) (4) (b) (4) *as indicated in SD63. Letters of Authorization to relevant DMF were provided.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Three lots are on primary stability and three lots are on supportive stability.

Reviewer comment*: Note that my review reflects the stability update provided on May 31, 2016.*

The shelf life of the drug product is currently set at 24 months when stored at the recommended temperature of 2-8°C. There is currently 24 months of real time stability data available for the primary (b) (4) mg/vial lots and 36 months for supportive lot G57332. Additionally, there is up to 60 months of additional supportive stability data (b) (4) As more stability data becomes available, the shelf life will be extended based on the suitability of the data.

To study the effects of temporary excursions from recommended storage condition, temperature cycling studies were included in the stability program. The drug product was subjected to 1

month of storage at -20 ± 5°C, and 12 months of storage at 25 ± 2°C/60 ± 5%RH. Additionally, the vials were reconstituted and stored at 2-8°C for 16 hours, to support temporary temperature excursions after vial reconstitution.

Reviewer comment*: Note that in addition to the accelerated stability study at 25 ± 2°C/60 ± 5%RH, lyophilized vials stored at 2-8°C for up to 24 months were reconstituted at each stability point, then stored at 2-8 ℃ for 16 hours before testing.*

Table 3.2.P.8.1-1. Primary Stability Study Lots

Lot Number	Dose Presentation	Site & Date of Manufacture	Intended Use	Storage Condition	Available Data
J10004	(b) (4) mg/vial in a 20 mL vial	Pearl River Apr 2014	• ICH Stability • Process Validation • Reference	2-8 °C	24 months (on-going)
				25 ± 2 °C/60 ± 5%RH	12 months (complete)
				2-8 °C for 16 hours after reconstitution	24 months (on-going)
H73259	(b) (4) mg/vial in a 20 mL vial	Pearl River Dec 2013	• ICH Stability • Process Validation	2-8 °C	24 months (on-going)
				25 ± 2 °C/60 ± 5%RH	12 months (complete)
				2-8 °C for 16 hours after reconstitution	24 months (on-going)
H73255	(b) (4) mg/vial in a 20 mL vial	Pearl River Nov 2013	• ICH Stability • Process Validation • Clinical (Phase 3)	2-8 °C	24 months (on-going)
				25 ± 2 °C/60 ± 5%RH	12 months (complete)
				2-8 °C for 16 hours after reconstitution	24 months (on-going)

Table 3.2.P.8.1-2. Supportive Stability Study Lots

Lot Number	Dose Presentation	Site & Date of Manufacture	Intended Use	Storage Condition	Available Data
G57332	(b) (4) mg/vial in a 20 mL vial	Pearl River Oct 2012	• Stability	2-8 °C	36 months (on-going)
				25 ± 2 °C/60 ± 5%RH	12 months (complete)
				2-8 °C for 16 hours after reconstitution	36 months (on-going)
F18455	(b) (4) mg/vial in a 20 mL vial	Pearl River Jun 2012	• Stability • Clinical (Phase 3)	2-8 °C	36 months (on-going)
F05275	(b) (4) mg/vial in a 20 mL vial	Pearl River Jan 2011	• Stability • Clinical (Phase 3)	2-8 °C	60 months (complete)

Table 3.2.P.8.1-4. Analytical Tests Used for the Stability Monitoring Programs

Attribute	Analytical Procedures used in the Supportive Studies	Analytical Procedures used in the Primary Studies	Proposed Analytical Procedures to be used in Commercial Studies

Characteristics	Appearance (Appearance of (b) (4) Appearance of Solution, & Reconstitution Time)	Appearance (Appearance of (b) (4) Appearance of Solution, & Reconstitution Time)	Appearance (Appearance of (b) (4) Appearance of Solution (Color, Clarity & Visible Particulates), & Reconstitution Time)
	pH	pH	pH
	Particulate Matter	Particulate Matter	Particulate Matter
	Moisture Content	Moisture Content	Moisture Content
	UV spectroscopy: Protein Content	UV spectroscopy: Protein Content	UV spectroscopy: Protein Content
	UV spectroscopy: Total Calicheamicin Derivative	UV spectroscopy: Total Calicheamicin Derivative	UV spectroscopy: Total Calicheamicin Derivative
	NA	UV spectroscopy: Drug to Antibody Ratio (DAR)	UV spectroscopy: Drug to Antibody Ratio (DAR)
Biological Activity	Immunoaffinity (Antigen Binding ELISA)	Immunoaffinity (Antigen Binding ELISA)	NA
	Cytotoxicity (Thymidine Uptake)	Cytotoxicity (Luminescence)/ Cytotoxicity (Thymidine Uptake)	Cytotoxicity (Luminescence)
Identity	Isoelectric Focusing	iCE (Conjugation Profile)	iCE (Conjugation Profile)
	SDS-PAGE (non-reducing)	CGE (non-reducing): Size Profile	NA
Purity/Impurity	NA	NA	CGE (non-reducing): Intact IgG
	SDS-PAGE (reducing)	CGE (reducing): Heavy Chain and Light Chain	CGE (reducing): Heavy Chain and Light Chain
	SE HPLC: Aggregates	SE HPLC: Aggregates	SE HPLC: Aggregates
	ELISA: Unconjugated Calicheamicin	ELISA: Unconjugated Calicheamicin	ELISA: Unconjugated Calicheamicin
	Low Conjugated Fraction (HIC)	iCE: Unconjugated mAb	NA
Safety	Sterility	NA	NA
	NA	CCIT	CCIT
	Endotoxin	NA	NA

Reviewer comment: *Note that some of the analytical tests used in the primary stability studies differ from the commercial tests. This is not expected to affect the validity of the primary stability studies as a basis of setting the expiration of the commercial product. See the method bridging studies in section 3.2. S.4.5, "Justification of Specifications".*

Table 3.2.P.8.1-7. Protocol for (b) (4) mg/vial Dose Lots at the Long Term Condition

Analytical Procedure	Time points (Months)									
	0	3	6	9	12	18	24	36	48	60
Appearance (Appearance of (b) (4), Appearance of Solution, & Reconstitution Time)	X	X	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X	X	X
Particulate Matter (subvisible)	X	X	X	X	X	X	X	X	X	X
Moisture Content	X	X	X	X	X	X	X	X	X	X
UV spectroscopy: Protein Content	X	X	X	X	X	X	X	X	X	X
UV spectroscopy: Total Calicheamicin Derivative	X	X	X	X	X	X	X	X	X	X
UV spectroscopy: Drug to Antibody Ratio (DAR)	X	X	X	X	X	X	X	X	X	X
Immunoaffinity (Antigen Binding ELISA)	X	X	X	X	X	X	X	NS	NS	NS
Cytotoxicity (Thymidine Uptake)	X	X	X	X	X	X	X	NS	NS	NS
Cytotoxicity (Luminescence)[a]	X	X	X	X	X	X	X	X	X	X
iCE: Conjugation Profile	X	X	X	X	X	X	X	X	X	X
CGE (non-reducing): Size Profile	X	X	X	X	X	X	X	X	X	X

CGE (reducing): Heavy Chain and Light Chain	X	X	X	X	X	X	X	X	X	X
SE-HPLC: Aggregates	X	X	X	X	X	X	X	X	X	X
Unconjugated Calicheamicin	X	X	X	X	X	X	X	X	X	X
iCE: Unconjugated mAb	X	X	X	X	X	X	X	NS	NS	NS
Container Closure Integrity Test (CCIT)	NS	NS	NS	NS	X	NS	X	X	X	X

NS = Not Scheduled
a. Tested as part of bridging study.

Reviewer comment*: The stability protocol under accelerated conditions (25 ± 2°C/60 ± 5%RH) is similar to that under long term conditions, except it runs for 12 months. The stability protocol at -20°C includes storage for 1 month as the only time point. The supportive stability protocols were also included, but not shown in my review.*

Photostability Study

Photostability of the (b) (4) mg/vial dose presentation from a process validation lot was studied. Vials were placed in a commercial package and exposed to ICH Q1B (option two) conditions of up to 1.2 million lux hours of light and 200 watt h/m^2 of near UV light at 25°C. Vials oriented horizontally for maximum light exposure were also exposed to the same light conditions without the packaging.

The secondary packaging provided adequate protection from the effects of light exposure specified in ICH Q1B. The studies support the recommended storage condition, "protect from light". When not protected by the secondary packaging, vials were susceptible to light induced degradation.

Reviewer comment*: The photostability protocol was provided and is adequate. The DP is sensitive to light; unconjugated calicheamicin levels are increased beyond specification after as low as 0.096 million lux hours light exposure, and cytotoxicity is moderately decreased. The secondary packaging provided adequate protection from light.*
In assessing stability, I considered the recommendations of OPB-RP-005 and ICH Q5C. Note that statistical analysis of the data is not included as the shelf life is based on real time stability data and no trends were observed; this is acceptable. Trending analysis of stability data related to aggregates, cytotoxicity, protein content, total calicheamicin, unconjugated calicheamicin, and water content was provided and indicated no clear trend or minimal trend. The stability program included at least three batches of final product representative of that used at manufacturing scale, fulfilling the recommendation of ICH Q5C. The proposed shelf life of 24 months at 2-8°C is acceptable.
In addition, stability data support temperature excursions of up to 1 month at -20 ± 5 ℃ and up to 12 months at 25 ± 2 ℃/60 RH. Reconstituted vials can be stored for up to (b) (4) *hours at 2-8°C, based on relevant stability data.*

3.2.P.8.2 Post-Approval Stability Commitment

Reviewer comment: *The post-approval stability protocol monitors samples for up to 60 months under long term conditions using adequate assays. Minimum one lot will be placed on stability each year the DP is manufactured. The proposed protocol is adequate.*

3.2.P.8.3 Stability Data

Reviewer comment: *Stability data were provided. At the intended storage temperature of 2-8°C, all results met specifications without a clear trend for up to 24 months. The product is stable for at least 24 months at 2-8°C, fulfilling the recommendation of ICH Q5C to provide at least 6 months stability data. At the accelerated storage temperature of 25 ± 2°C/60 RH, all results met specifications without a clear trend for up to 12 months, although unconjugated calicheamicin levels and moisture content increased slightly. Stability results for lyophilized vials that were stored at 2-8°C for up to 24 months, then reconstituted at each stability point and stored at 2-8°C for 16 hours before testing met specifications without a clear trend.*

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Reviewer comment: *This section is not reviewed by OBP.*

3.2.A.2 Adventitious Agents Safety Evaluation

The adventitious agent control program includes (b) (4)

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No validation report for viral clearance was provided in the BLA. Provide the complete virus removal study report. In addition, provide data demonstrating that the manufacturing process (b) (4) used in the virus removal study were representative of the product.

The following response was received in SD52 on May 24 (abbreviated).
The validation reports pertaining to viral clearance studies are provided within the supporting documentation. The clinical manufacturing process (b) (4) used for the (b) (4) virus validation studies were subsequently used to manufacture (b) (4) batches. Therefore, the (b) (4) used for the (b) (4) studies are considered to be representative of the product.

Reviewer's comment*: The validation reports were provided. Justification was provided that the manufacturing process* (b) (4) *used in the virus removal study were representative of the product. The response is acceptable.*

3.2.A.3 Novel Excipients

Reviewer comment: *This section was not provided, as there are no novel excipients.*

3.2.R Regional Information
3.2.R.1 Executed Batch Records

(b) (4)

3.2.R.2 Method Validation Package

Reviewer comment*: Appropriate sections of the submission are referenced for relevant data.*

3.2.R.3 Comparability Protocols

Reviewer comment*: This section was not provided; there are no comparability protocols.*

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Reviewer comment*: Based on the clinical summary, 1.8% of ALL patients (4 patients total) were detected ADA positive pre-dose, and 0.9% of ALL patients (2 patients total) were detected ADA positive post-dose only. In ALL clinical studies, ECL and cell-based assays were used to detect ADA and nAb, respectively. My review of these immunogenicity assays are below.*
In PK studies in NHL patients, ELISA methods were used to detect ADA. Because the current BLA is for ALL indication, I did not review of the immunogenicity assays used in PK studies in NHL patients.

Validation of an ECL Method for the Detection of Anti-PF-05208773 Antibodies in Human Serum (Validation report B1937005; performed by (b) (4)

Human serum samples, positive controls and negative controls are diluted with assay buffer and co-incubated with biotinylated and ruthenylated inotuzumab ozogamicin on a microtiter plate. ADA binds to both labeled inotuzumab ozogamicin molecules to form a complex. After incubation, 50 µL of each mixture is added to wells of an Avidin High Bind MSD plate and allowed to bind for 2 hours. In the presence of read buffer, ruthenium produces a chemiluminescent signal.

Summary of Validation Study Results – ADA Assay

Inter-Run Precision of PC1	1.2%
Intra-Run Precision of PC1	0.7%
Intra-Day Precision of PC1	0.8%
PC1 End Point Titer Acceptance Criteria	3.71 - 4.67
Negative control Acceptance Criteria	<161 RLU
Plate Cut Point Factor for Screening in ALL	1.47
Confirmation Cut Point in ALL (inotuzumab ozogamicin)	59.4%
Confirmation Cut Point in ALL (inotuzumab)	12.8%
Confirmation Cut Point in ALL (calicheamicin-BSA)	63.8%
Matrix Selectivity (Recovery) with PC1	Low PC: 90% lots recovered 75-125% High PC: 90% lots recovered 75-125%
Matrix Selectivity (Recovery) with PC2	Low PC: 90% lots recovered 75-125% High PC: 90% lots recovered 75-125%
Drug Tolerance with PC1 (LPC-750x diluted)	<5 µg/mL inotuzumab ozogamicin
Drug Tolerance with PC1 (HPC-75x diluted)	<50 µg/mL inotuzumab ozogamicin
Mass-based Sensitivity - Purified anti-inotuzumab	215 ng/mL
PC1 Room Temperature Stability in Serum	≥23 hours at room temperature
PC1 Freeze/Thaw Stability in Serum at -70°C	≥5 freeze/thaw at -70°C
PC1 Freeze/Thaw Stability in Serum at -20°C	≥5 freeze/thaw at -20°C
PC2 Room Temperature Stability in Serum	≥23 hours at room temperature
PC2 Freeze/Thaw Stability in Serum at -70°C	≥5 freeze/thaw cycles at -70°C
PC2 Freeze/Thaw Stability in Serum at -20°C	≥5 freeze/thaw cycles at -20°C
Biotinylated and Ruthenylated inotuzumab ozogamicin Freeze/Thaw Stability	≥5 cycles at -70°C

PC1, anti-inotuzumab; PC2, anti-calicheamicin

***Reviewer comment**: The validation report was provided. The negative control in the assay is pooled normal human serum. The positive controls are anti-inotuzumab (PC1) and anti-calicheamicin (PC2) Abs. The instrument is from Meso Scale Discovery and the software used was also specified. Detailed methodology and data were provided and are summarized below.*

Precision for Primary and Secondary PC

Precision of the method was expressed as the coefficient of variation (%CV) from analyzing replicates of anti-inotuzumab (PC1). The intra-run precision was determined from one set of NC and 5 sets of PC1 on each plate. The intra-run precision of the endpoint log10 titers is 0.7%. The intra-day precision was determined from one set of NC and 5 sets of PC1 on four separate plates.

The intra-day precision of the NC is 2.8% and for PC1 the precision for the endpoint log10 titer is 0.8%.

The inter-run precision for PC1 was determined from all 59 accepted analytical runs, performed by 5 analysts. The inter-assay precision of maximum PC RU, endpoint log10 titer, mean negative control responses and plate cut point are 12.3%, 1.2%, 6.3% and 6.3%, respectively. Intra-run, intra-day and inter-run precisions met the acceptance criteria.

Screening and Confirmatory Cut Point Determination

Assay response for 50 ALL serum samples not exposed to inotuzumab ozogamicin was evaluated. The samples were diluted 200-fold. The cut point value was determined based on 95% upper confidence limit after removal of statistical outliers. Each sample was tested in 3 independent runs completed by two analysts. The average calculated plate cut point factors for the screening runs is 1.47.

During validation, serum samples were incubated in the presence or absence of inotuzumab ozogamicin and then diluted 1:200 for analysis. The PC1 HPC and LPC controls were also tested with and without the presence of inotuzumab ozogamicin. For the HPC and LPC, the mean RU decreased by an average of 95.5% and 78.2%, respectively, in the presence of inotuzumab ozogamicin. A confirmatory cut point of 59.4% inhibition with inotuzumab ozogamicin was established based on a 0.1% false positive rate.

The serum samples were also incubated in the presence or absence of inotuzumab and then diluted 1:200 for analysis. The PC1 HPC and LPC controls were also tested with and without the presence of inotuzumab. For the HPC and LPC, the mean RU decreased by an average of 96.8% and 76.3%, respectively, in the presence of inotuzumab. A confirmatory cut point of 12.8% inhibition with inotuzumab was established based on a 0.1% false positive rate.

Additionally, the serum samples were incubated in the presence or absence of calicheamicin -BSA and then diluted 1:200 for analysis. The PC2 HPC and LPC controls were also tested with and without the presence of calicheamicin-BSA. For the HPC and LPC, the mean RU decreased by an average of 94.5% and 65.9%, respectively, in the presence of calicheamicin-BSA. A confirmatory cut point of 63.8% inhibition with calicheamicin -BSA was established based on a 0.1% false positive rate. For all three confirmatory cut point evaluations, the runs were completed by at least two analysts over at least 2 days.

Stability

Room temperature stability of PC1 and PC2 Abs in human serum was assessed. PC aliquots were thawed and kept at room temperature for ~23 hours and then stored at -70°C until the assay. Samples were analyzed together with an aliquot of the PC that was thawed immediately before analysis. The stored PCs were within the acceptance criteria.

Freeze/thaw stability of PC1 and PC2 Abs in human serum was assessed. PC samples were frozen at -70°C or at -20°C (for ≥24 hours for the first cycle and ≥12 hours for the other cycles) and thawed unassisted at room temperature. Samples were analyzed after completion of the fifth

cycle together with an aliquot of the PC that was thawed before analysis. The 5 freeze/thaw cycle stabilities of PC1 and PC2 at both -70°C at -20°C were within the acceptance criteria.

Biotinylated and Ruthenylated inotuzumab ozogamicin samples were frozen for ≥24 hours at -70°C and then subjected to 5 freeze/thaw cycles. The difference of the PC endpoint log10 titer between treated and untreated samples was 0.2, suggesting that Biotinylated and Ruthenylated inotuzumab ozogamicin are both stable for at least 5 freeze/thaw cycles at -70°C.

Matrix Selectivity (Recovery)
Recovery is the ability of the method to differentiate and quantify the analyte in the presence of other components. The assay recovery was performed by analyzing ten lots of ALL human serum samples spiked with HPC1 and LPC1 (anti-inotuzumab), or with HPC2 and LPC2 (anti-calicheamicin). For each category, ≥90% of the spiked lots had a recovery between 75-125%.

Drug Interference (Tolerance)
The concentration of inotuzumab-ozogamicin that inhibits the ability to detect the positive control was assessed. PC1 (anti-inotuzumab) was pre-incubated with different concentrations of inotuzumab-ozogamicin. The test was performed using anti-inotuzumab at HPC (1:75) and LPC (1:750), and inotuzumab-ozogamicin at 0, 1, 5, 10, 20, and 50 µg/mL. The highest concentration of inotuzumab-ozogamicin in which the positive control was greater than the plate cut point was identified. Anti-inotuzumab at 1:75 and 1:750 can tolerate at least 50 µg/mL and 5 µg/mL of inotuzumab-ozogamicin, respectively.

Reviewer comment*: The concentration of the PC1 (anti-inotuzumab) stock is 2.07 mg/ml, therefore the 75-fold dilution corresponds to 27.6 µg/ml and the 750-fold dilution to 2.76 µg/ml. The assay was determined to tolerate 50 µg/mL of inotuzumab-ozogamicin with 27.6 µg/ml of anti-inotuzumab; and 5 µg/mL of inotuzumab-ozogamicin with 2.76 µg/ml of anti-inotuzumab – corresponding to 1.8-fold excess inotuzumab-ozogamicin at both conditions. According to section 2.7.2 Summary of Clinical Pharmacology, the maximum mean inotuzumab ozogamicin serum concentration in patients was 335 ng/ml by cycle 4, when steady-state exposure was reached. Therefore, the drug tolerance of the assay appears adequate. Drug interference was not assessed using PC2 (anti-calicheamicin).*

Mass-based Assay Sensitivity
Mass-based assay sensitivity is the concentration of ADA in serum that will result in a signal equal to the plate cut point. For affinity purified anti-inotuzumab, it was calculated to be 215 ng/mL.

Sample Analysis Acceptance Criteria Determination
Samples will be screened first using tier 1 assay. A sample is considered tier 1 positive if the signal is equal to or greater than the plate cut point. To accept samples, the %CV of duplicates must be ≤25%.

Tier 1 positive samples will be assessed with tier 2 confirmatory analysis (inotuzumab-ozogamicin immune-competition). Tier 2 positive samples will be assessed with End Point Titer

analysis (tier 3). Tier 2 positive samples will also proceed with tier 4 cross-reactivity analysis (inotuzumab and calicheamicin-BSA cross-reactivity).

***Reviewer comment**: A list of controls and acceptance criteria was provided for both the primary and confirmatory assays. The confirmatory assay will include controls containing PC1 (anti-inotuzumab; at both HPC and LPC) in the presence or absence of inotuzumab. The confirmatory assay will also include controls containing PC2 (anti-calicheamicin; at both HPC and LPC) in the presence or absence of calicheamicin-BSA. The controls are appropriate.*

Validation of a Cell Based Assay for the Detection of Neutralizing Anti-PF-05208773 Antibodies in Human Serum (Validation report B1937004; performed by (b) (4) (b) (4)

The RS4;11 B cell line at 10^4 cells in 80µL per well is incubated with 100 µg/mL PF-05208773 (CMC-544) and samples for 24±1 hours. Antibodies that neutralize the drug activity will protect the cells from killing. After the incubation, cells are lysed using CellTiter- Glo® Luminescent Cell Viability kit and the luminescence is recorded with a SpectraMax L microplate reader. The kit determines the number of viable cells based on the quantitation of ATP; therefore the response generated corresponds to the amount of viable cells. The signals generated from the viable cells are directly proportional to the amount of neutralizing antibodies present in the sample. Data are presented as end point log10 titers, defined as the reciprocal of the serum dilution at which the sample response would be equal to the cut point of the assay. Experiments were conducted to assess assay screening cut points, precision, selectivity (recovery), drug tolerance, sensitivity, dilution linearity, robustness and stability.

Summary of Validation Study Results – Cell Based nAb Assay

PC Inter-Assay Precision	9.3%
PC Intra-Run Precision	6.1%
PC Intra-Day Precision	9.2%
PC log10 titer acceptance	1.20 - 2.13; derived from inter-assay precision runs
Cut Point Factor for screening	1.24
Cut Point Factor for titration	1.24
Screening Cut Point	Mean NC of the plate × 1.24
NC Acceptance Range	307000 – 1020000 RU; Derived from inter-assay precision
Drug Tolerance Test	PC1 (1:250) – Maximum 1 µg/mL
Matrix Selectivity (Recovery) in ALL human serum	Unspiked samples generated signal below the cut point. 100% of lots with reportable results had recovery of 70-130%.
Assay Sensitivity	58.3 ng/mL using PC
PC Stability in Human Serum	At least 21 hours at room temperature
PC Freeze/Thaw Stability in Human Serum	At least 5 Cycles at -20°C At least 5 Cycles at -70°C

Cell Line Passage Stability	Assay performance at cell passage number ≤ 10 or ≥ 20 acceptable

Assay Precision

Precision was expressed as the coefficient of variation (%CV) from analyzing replicates of PC. The intra-run precision was determined from one set of NC and 8 independent titrations of the same starting stock solution of PC. The precision for the PC was determined from all 8 titration samples tested on the same plate to be 6.1%. The intra-day precision was determined from one set of NC and plate-independent sets of titrated PC at n=5 on four plates. The precision was determined from all PC samples analyzed across the four plates to be 9.2%. The inter-run precision was determined from 23 applicable analytical runs. The %CV of PC endpoint log10 titer is 9.3%.

Screening Cut Point Determination

Screening cut point was evaluated by testing 50 ALL human serum samples. The cut point value was determined based on 95% upper confidence limit. Individual samples were analyzed at minimum of 3 independent runs on at least 2 days with two or more analysts. Data from all 3 batch runs were normally distributed. The average calculated screening plate cut point factor for the screening runs is 1.24 based on 99% confidence intervals.

Stability of Positive Control

Room temperature stability of PC1 (1:250) in human serum was used as the surrogate to evaluate nAb stability. The stability of PC1 (1:250) in human serum was used as the surrogate to evaluate nAb stability in the matrix after 5 freeze/thaw cycles. Individual PC1 samples were frozen at -20°C or at -70°C for a minimum of 24 hours for the first cycle and a minimum of 12 hours for subsequent cycles, and thawed at room temperature for at least 1 hour between frozen periods.

Matrix Selectivity (Recovery)

The assay recovery was performed by analyzing NC, assay buffer and 12 individual lots of ALL human serum spiked with and without PC1 (1:250). All unspiked samples generated signal below the cut point showing negative result. A 100% of the ALL lots with reportable results had recovery of 70-130%.

Drug Interference (Tolerance)

PC1 (1:250) was pre-incubated with PF-05208773 at different concentrations (0, 0.063, 0.125, 0.25, 0.5, 1, 2 and 4 µg/mL). The highest concentration of PF-05208773 where the PC is greater than the plate cut point was identified to be 1 µg/mL. The data suggests that nAb can be detected in the presence of ≤1 µg/mL of circulating inotuzumab ozogomicin.

Mass-based Assay Sensitivity

Mass-based assay sensitivity is the concentration of PC that results in a signal equal to the plate cut point. Based on the 3 independent runs from 2 analysts, the assay sensitivity is calculated as the mean of the PC concentration at the ACP, which is 58.3 ng/mL.

Cell Passage Stability

Cell passage stability is evaluated with 2 independent runs. Each run includes 2 passages of cells with the same NC and PC preparations on the same plate. On each plate, one cell passage is ≤ 10 (passage 9 and 10), and the other one is ≥ 20 (passage 21 and 22). The result of late passage cells was within 100 ± 25% of that from the early passage cells.

Sample Analysis Acceptance Criteria Determination

Based on the results from the validation, the following are the sample analysis acceptance criteria. For a sample analysis run, the following controls are included, (1) eight NC (single reading), (2) one PC (duplicate readings) - initial dilution of 1:250 and 7 more two-fold serial dilutions. Mean NC response must be within 307000 - 1020000 (mean NC response ± 2 SD). Maximum two NC outlier value can be excluded in case of high variability (%CV ≥ 30). A screening cut point factor of 1.24 is used.

Samples can be simultaneously tested in screening and titration, or can be directly tested in titration assay. In the latter case, data from the first dilution will be used to determine whether a sample is positive. A sample is considered tier 1 positive if the mean signal is equal to or greater than the plate cut point. To accept samples, the %CV of duplicates must be 30% or less if at least one measurement is above the plate cut point, otherwise the sample will be re-assayed. Tier 1 positive samples will proceed with tier 2 end point titer analysis. If tier 1 is positive, but tier 2 EPT is negative, the final result will be reported as positive. Otherwise, the sample will be reported positive with an end point log10 titer.

***Reviewer comment**: The validation report was provided. The negative control in the assay is pooled normal human serum. The positive control is rabbit anti-G544 polyclonal antibody at 250-fold dilution. The minimum required sample dilution is 10-fold. Detailed methodology and data were provided. According to section 2.7.2 Summary of Clinical Pharmacology, the maximum mean inotuzumab ozogamicin serum concentration in patients was 335 ng/ml; therefore, the drug tolerance of the assay appears adequate.*

The following deficiencies were identified and communicated to Sponsor on May 9, 2017 regarding the immunogenicity assay (Question 6).

Regarding the ECL method used to detect anti-product antibodies in human serum:

a. Justify the selection of 200-fold as the minimum required sample dilution. FDA recommends that dilutions not exceed 100-fold; for higher dilutions the overall effect on assay sensitivity and immunogenicity risk assessment should be considered (Draft guidance for industry, Assay development and validation for immunogenicity testing of therapeutic products, https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf)

b. Provide the mass-based sensitivity of the confirmatory assay. FDA's expectation is that the confirmatory assay is at least as sensitive as the screening assay, but with higher specificity (ibid).

c. Justify the concentration of the anti-inotuzumab low positive control which, based our calculations, contains 2.76 µg/ml anti-product antibodies. Note that FDA recommends a low positive control containing a concentration of anti-product antibodies slightly above the sensitivity of the assay, to ensure consistent assay sensitivity across runs (ibid).

d. Provide the mass-based sensitivity of the assay for the anti-calicheamicin positive control. As calicheamicin may be immunogenic, it is important to assess that the assay is able to

sensitively detect antibodies against calicheamicin. In addition, justify in relation to the mass-based sensitivity of the assay, that the anti-calicheamicin low positive control is used at an appropriate concentration (see note to question 6c).

e. No justification was provided regarding the concentrations of spiked inotuzumab ozogamicin, inotuzumab and CMC-BSA chosen for the tier 2 confirmatory analysis. We note that inotuzumab is spiked at a particularly high concentration, potentially leading to non-specific effects. Provide a rationale indicating that the concentrations of the spiked proteins are appropriate to confirm the presence of antibodies throughout and above the range of the assay.

f. Provide a complete description and evaluation of the tier 3 End Point Titer analysis.

The following response was received in SD52 on May 24, 2017 (abbreviated).

Response to question 6a (abbreviated)
Preliminary development work was conducted in normal human serum. Thirty seven normal human serum samples were tested at final dilutions of 1:50, 1:100 and 1:200.

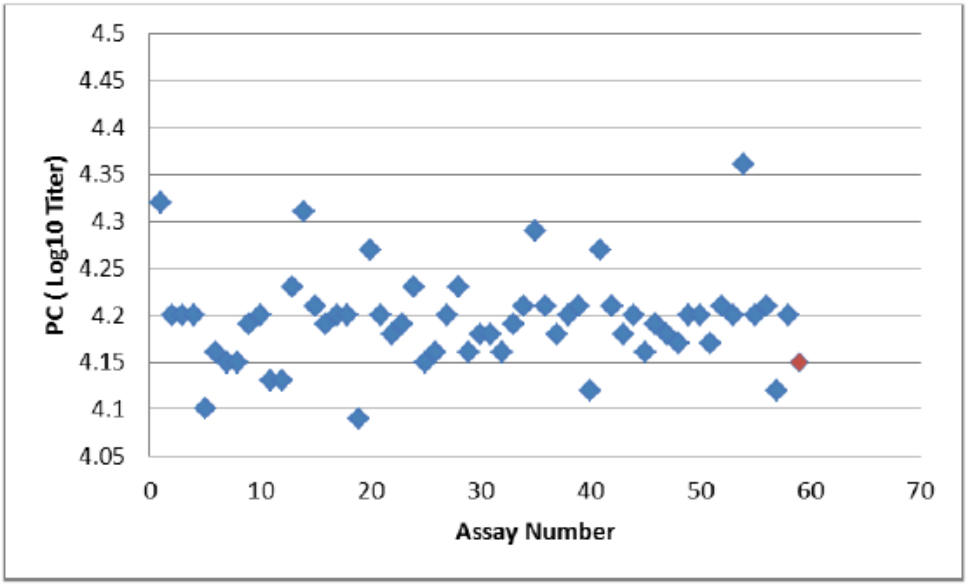
Reviewer's comment*: Relevant data were provided. Variability was lowest at 200-fold sample dilution. Overall, the assay appears sufficiently sensitive; therefore there is no need to change the sample dilution factor. The response is acceptable.*

Response to question 6b (abbreviated)
The mass based sensitivity of the confirmatory assay was considered identical to the screening assay, 215 ng/mL, since the same method and platform were utilized. Positive ADA results are based on statistically derived cutpoints and are not necessarily of clinical significance. The sensitivity of the confirmatory assay is based on a statistically derived cutpoint and signal of a surrogate positive control.

Reviewer's comment*: Additional justification and data were provided. I agree that the sensitivities of the screening and confirmatory assays are linked, also noting that the inhibitory cutpoints in the confirmatory assay were statistically derived. The response is acceptable.*

Response to question 6c (abbreviated)
In the method, a titrated positive control was included in the screening, confirmatory, and titer assays and the end point titer of the positive control was determined by interpolation at the assay cutpoint. During validation, the acceptance criteria were established for sample analysis based on ±1 dilution factor of the PC titration. By basing assay acceptance criteria on the PC end point titer, consistent sensitivity was ensured across runs (Figure 2). As an additional point of clarification, the mass based sensitivity of the screening assay was calculated using affinity purified antibodies against drug in contrast to the LPC which is a polyclonal rabbit serum.

Figure 2. Consistent Performance of Log10 Titer of PC During Validation (n=59)



Red symbol indicates the Log_{10} titer of PC from sensitivity run where affinity purified antibody was titrated to provide sensitivity of 215 ng/mL.

A LPC with a dilution of 1:750 was selected based on approximately 2 times the upper limit of NC RLU signal determined during validation. The LPC response was normally distributed with no outliers over the 30 replicates during method validation and sample analysis. Considering the upper limit of NC signal (161 RLU) and variability of naïve individual ALL serum samples, the Sponsor considers the dilution of 1:750 of LPC providing signal response of approximately 311 RLU to be justified.

Reviewer's comment*: It appears that every assay run includes a titrated positive control, with ±1 dilution factor of the titration as an assay acceptance criterion; this needs to be confirmed. If this is true, this would be an appropriate control to ensure consistent assay sensitivity across runs, and could substitute for a sensitive low positive control. Pfizer clarified that an affinity purified antibody sample was used to establish the mass based sensitivity of the assay, however the positive control used during the rest of assay validation was diluted serum. Figure 2 appears to suggest that assay sensitivities obtained with affinity purified antibody and diluted positive control are comparable. However, clarification is needed regarding calculation of the log10 titer for the affinity purified antibody sample in Figure 2, which could have included the fold purification factor for the affinity purified antibody sample.*

Response to question 6d (abbreviated)

As sensitivity value is entirely dependent upon the nature of the positive control and thus numerically has little relevance with the assay ability to detect true human responses. Two lots of (b) (4) purified anti-calicheamicin antibodies were tested. The sensitivity for the first lot was 5 µg/mL; sensitivity of the second lot was 2 µg/mL. Both antibodies were purified using (b) (4)

(b) (4) The large quantities of unrelated IgG found in these preparations account for considerably higher sensitivity when compared to affinity purified primary antibody.

During sample testing, anti-product antibodies were detected in 6 ALL patients. Additional specificity testing of these confirmed ADA responses demonstrated specificity to calicheamicin. Overall, the validation and sample testing data confirmed that the assay was capable of detecting antibodies to calicheamicin.

Reviewer's comment*: I agree that assays using* (b) (4) *-purified control antibodies underestimate sensitivity. Actual detection of anti-product Abs in patient samples suggests that the assay performs reasonably well.*

Response to question 6e (abbreviated)

Concentration of inotuzumab ozogamicin

In the confirmatory assay, samples are diluted in the presence and absence of 10 µg/mL inotuzumab ozogamicin. This concentration was selected based on early development work. At inotuzumab ozogamicin concentrations of 0-100 µg/mL, concentration dependent inhibition of polyclonal PC was demonstrated. Maximal signal inhibition of the PC was observed starting at 10 µg/mL and was selected for confirmatory analysis.

Concentration of inotuzumab

The Sponsor acknowledges that a high inotuzumab concentration was used. A concentration of 10 µg/mL consistent with the inotuzumab ozogamicin confirmatory assay was originally intended; however, an error in understanding the starting concentration of inotuzumab resulted in an actual concentration of 320 µg/mL.

Concentration of CMC-BSA

To compensate for the molar difference of inotuzumab ozogamicin (150 kDa) versus CMC- BSA (66 kDa), the CMC-BSA concentration was doubled at 21 µg/mL to account for differences in molecular weight and maintain equivalent protein concentration.

Reviewer's comment*: Results were provided for determining the optimal concentration of inotuzumab ozogamicin. The concentrations of inotuzumab ozogamicin and CMC-BSA used in the assay are sufficiently justified. The high concentration of inotuzumab used in the assay is the result of an error. See new IR to obtain information regarding the sensitivity of the confirmatory assay and to assess the likelihood of false negative samples.*

Response to question 6f (abbreviated)

For confirmed positive samples, End point titer was determined by diluting samples 1:100 assay buffer and then serially diluted 3-fold. A sample's titer was determined by interpolation of the dilution at the assay cutpoint using the screening cutpoint factor (≥1.47). End point titer analysis was validated using polyclonal rabbit anti-G544 serum as a surrogate positive control. During validation, precision of PC end point log10 titer was evaluated and expressed as the coefficient of variation (%CV). The intra-run precision was determined from 5 sets of independently titrated anti-G544 on each intra-run plate. The intra-run precision of the End point log10 titers was calculated as 0.7% CV. The intra-day precision was determined from 5 sets of anti-G544 on four

separate plates. The PC analyzed on each plate was an independent PC titration. The resulting precision for the End point log10 titer was 0.8%CV. The inter-run precision of the assay for anti-G544 was also determined from all 59 accepted validation analytical runs, which were run by 5 analysts. The results for inter-assay precision of End point log10 titer was 1.2% CV. For sample testing, 38 assays were run generating mean log10 EPT of 4.17 (3.1%CV; titers ranged from 3.71 to 4.48) which was within acceptance range (log10 titer 3.71 to 4.67) calculated from validation runs.

Reviewer's comment*: Additional details were provided. The response is adequate.*

The following IR was sent to Sponsor on June 6, 2017.

Regarding your IR response dated May 24, 2017 to question 6 about the ECL method used to detect anti-product antibodies in human serum:

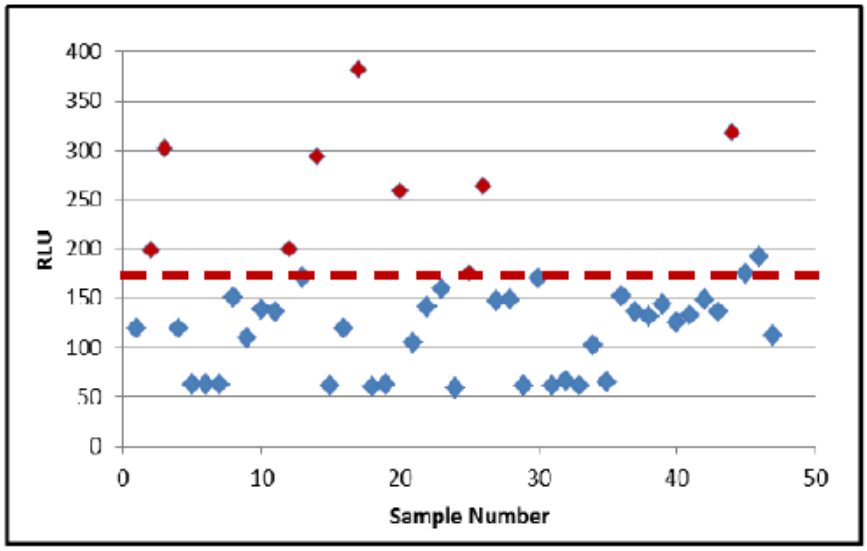
1. The sensitivity of the confirmatory ECL method is unclear. In order to assess the likelihood of false negative samples in the confirmatory assay, provide the number of ALL patient samples that were positive in the screening assay, but were negative in the confirmatory assay. For those samples that were confirmed positive, provide the end point titers obtained in the tier 3 analysis.
2. Based on your response to question 6c, our understanding is that every assay run includes a titrated positive control, with a ±1 dilution factor of the titration as an assay acceptance criterion. Please confirm or provide clarification. In addition, since Figure 2 provides the log10 titers of the serum-based unpurified Positive Controls, explain how the log10 titer was calculated for the affinity purified antibody sample, and provide the level or fold purification that was achieved.

The following response was received in SD56 on June 13, 2017 (abbreviated).

Response to question 1 (abbreviated)

In Study B1931022, 47 out of 548 samples (8.58%) were tested positive in the screening assay. In the confirmatory assay, 38 out of these 47 samples tested negative for ADAs and 9 samples tested positive. The signal response of 47 samples ranged from 60-382 RLU as shown in Figure 1, with % inhibition ranging from 0-81%.

Figure 1. Assay Signal Response of Unspiked Samples in Confirmatory Assay (n=47)



Acceptance Limit of Negative Control RLU (161 RLU)

Red markers denotes confirmatory positive samples(n=9)

Reviewer's comment*: The end point log titers of the confirmed positive samples were provided (not included in my review). The percentage of samples that was found positive in the confirmatory assay is within the anticipated range, considering the statistically determined cut point. The response is acceptable.*

Response to question 2 (abbreviated)

The Agencies' understanding is correct; for every sample analysis run (i.e. plate), a primary positive control was titrated, with a ±1 dilution factor of the titration as an assay acceptance criterion. The endpoint log10 titer was consistently determined for purified or unpurified positive control and for any samples that required titration. For the titration, the titer was first calculated as a dilution factor and then the titer was reported as a Log10 value.

The purification of polyclonal rabbit serum was performed in two steps. The first step utilized resin coupled with an irrelevant unrelated antibody followed by ligand affinity purification of the specific anti-G544 antibodies. Assuming 10 mg/mL total IgG, the purified antibody yield was 3.73% from 10 mL of rabbit serum.

Reviewer's comment*: Inclusion of a titrated positive control in every assay run is a useful control that assures comparable assay sensitivity across runs. The purification report was provided as a new supporting document. Purification of the positive control antibody was adequate and the purification yield is reasonable. The provided concentration of the purified high titer positive control (2.07 mg/ml), and the stated mass based sensitivity of the assay (215 ng/ml) correlates with the approximately 4 log10 titer shown for the purified positive control. The response is acceptable.*

Mate Tolnay

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Date: 6/28/2017 04:44:23PM
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Gerald Feldman

Digitally signed by Gerald Feldman
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Joel Welch

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