

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761029Orig1s000**

**CHEMISTRY REVIEW(S)**



First Approval for Indication

**Recommendation:**

**BLA: Approval**

## BLA 761029 Review 1

<b>Drug Name/Dosage Form</b>	ZINBRYTA (daclizumab)/Pre-filled Syringe
<b>Strength</b>	150 mg/mL
<b>Route of Administration</b>	Subcutaneous every 4 weeks
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Biogen Idec
<b>US agent, if applicable</b>	Not Applicable

- a. Names
  - i. Proprietary Name: Zinbryta
  - ii. Trade Name: Zinbryta
  - iii. Non-Proprietary/USAN: daclizumab
  - iv. INN Name: daclizumab
  - v. Other: None
  - vi. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P01589 (IL2RA\_HUMAN)
- b. Pharmacologic category: Therapeutic recombinant humanized monoclonal antibody

### Product Overview

Zinbryta (daclizumab) is a recombinant humanized IgG1 antibodies produced in NS0 cells. Daclizumab specifically binds to CD25, the alpha subunit of the human high-affinity interleukin-2 receptor. IL-2 receptor is a heterotrimeric protein expressed on the surface of certain immune cells, such as lymphocytes, that binds IL-2. Daclizumab prevents binding of IL-2 to CD25, subsequently inhibits IL-2 signaling, including IL-2 induced T cell proliferation and activated T cell responses. Daclizumab also induces a low level of antibody dependent cellular cytotoxicity. For additional information see Appendix A of the initial integrated review memo.

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Chen Sun	Division of Biotechnology Review and Research - II
Drug Product	Chen Sun	Division of Biotechnology Review and Research – II
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	Colleen Thomas	Division of Microbiology Assessment
Facility	Wayne Seifert	Division of Inspectional Assessment
Immunogenicity	Chen Sun	Division of Biotechnology Review and Research - II
Regulatory Business Process Manager	Anita Brown	OPRO
Application Technical Lead	Joel Welch	Division of Biotechnology Review and Research – II
Microbiology Team Lead	Patricia Hughes	Division of Microbiology Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment

**Cross-Discipline Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
RPM	Laurie Kelley	ODE 1/DNP
CDTL	John Marler	ODE 1/DNP
Medical Officer	Larry Rodichok	ODE 1/DNP
Medical Officer	Lourdes Villalba	ODE 1/DNP
Clinical Pharmacology	Ta Chen Wu	DCPII
Statistics	Xiang Ling	ODE 1/DNP
Pharm/Tox	David Carbone	DBVI

**Quality Review Team – Signature Page**

DISCIPLINE	REVIEWER	SIGNATURE
Drug Substance	Chen Sun	Chen Sun -S <small>Digitally signed by Chen Sun S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chen Sun S 0 9 2342 19200300 100 1 1-0010409028 Date: 2016 04 18 08:53:38 -0400</small>
Drug Product	Chen Sun	Chen Sun -S <small>Digitally signed by Chen Sun S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chen Sun S 0 9 2342 19200300 100 1 1-0010409028 Date: 2016 04 18 08:54:14 -0400</small>
Microbiology Drug Substance	Bo Chi	Bo Chi -S <small>Digitally signed by Bo Chi S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bo Chi S 0 9 2342 19200300 100 1 1-1300194820 Date: 2016 04 18 12:02:00 -0400</small>
Microbiology Drug Product	Colleen Thomas	Colleen Thomas -S <small>Digitally signed by Colleen Thomas S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Colleen Thomas S 0 9 2342 19200300 100 1 1-2000334597 Date: 2016 04 18 13:10:35 -0400</small>
Facility	Wayne Seifert	Wayne E. Seifert -S <small>Digitally signed by Wayne E. Seifert S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People 0 9 2342 19200300 100 1 1-2001599284 cn=Wayne E. Seifert S Date: 2016 04 19 05:24:22 -0400</small>
Immunogenicity	Chen Sun	Chen Sun -S <small>Digitally signed by Chen Sun S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chen Sun S 0 9 2342 19200300 100 1 1-0010409028 Date: 2016 04 18 08:55:05 -0400</small>
Regulatory Business Process Manager	Anita Brown	
Application Technical Lead/DS and DP Team Leader	Joel Welch	Joel T. Welch -S <small>Digitally signed by Joel T. Welch S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch S 0 9 2342 19200300 100 1 1-2004443745 Date: 2016 04 16 08:29:52 -0400</small>
Microbiology Team Lead	Patricia Hughes	Patricia F. Hughestroost -S <small>Digitally signed by Patricia F. Hughestroost S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People 0 9 2342 19200300 100 1 1-1300090507 cn=Patricia F. Hughestroost S Date: 2016 04 18 12:10:50 -0400</small>
Facilities Team Lead	Peter Qiu	Zhihao Qiu -S <small>Digitally signed by Zhihao Qiu S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu S 0 9 2342 19200300 100 1 1-2000438274 Date: 2016 04 18 20:51:38 -0400</small>
OBP Branch Chief	Juhong Liu	Juhong Liu -S <small>Digitally signed by Juhong Liu S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Juhong Liu S 0 9 2342 19200300 100 1 1-0010409157 Date: 2016 04 18 11:19:06 -0400</small>

## Quality Review Data Sheet

### 1. LEGAL BASIS FOR SUBMISSION: 351(a)

### 2. RELATED/SUPPORTING DOCUMENTS:

#### B. Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
761029/0000	February 27, 2015	N/A
761029/0.07	April 8, 2015	OBP, DMA, DIA
761029/0.22	July 1, 2015	OBP, DMA, DIA
761029/0.37	Sept 25, 2015	OBP
761029/0.43	November 5, 2015	OBP
761029/0.47	December 8, 2015	OBP
761029/0.48	December 14, 2015	DMA
761029/0.49	January 7, 2016	DMA
761029/0.52	January 19, 2016	DMA
761029/0.53	January 27, 2016	OBP, DMA
761029/0.54	January 29, 2016	DMA
761029/0.56	February 08, 2016	DMA
761029/0.62	March 02, 2016	DMA
761029/0.64	March 07, 2016	DMA
761029/0.69	March 21, 2016	DMA
761029/0.70	March 24, 2016	DMA
761029/0.71	March 25, 2016	DMA
761029/0.74	April 12, 2016	DMA
761029/0.75	April 13, 2016	DMA

#### C. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	3	Adequate	N/A	N/A
	Type III			3	Adequate	N/A	N/A

(b) (4)	Type III	(b) (4)	3	Adequate	N/A	N/A
	Type III		1	Adequate	March 2 2016	Reviewed by C. Thomas

<sup>1</sup> 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")

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

**D. Other Documents:** None

**3. CONSULTS:** None.

## Integrated Review

**I. Recommendations**

The Office of Pharmaceutical Quality recommends approval of BLA 761029 for Zinbryta (daclizumab) manufactured by Biogen Idec, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Zinbryta (daclizumab) 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.

**A. Recommendation and Conclusion on Approvability**

The DS and DP manufacturing process is well controlled and should consistently deliver DS and DP of desired quality.

A PMR is recommended as the the current method for detecting neutralizing anti-drug antibodies (ADA) is not tolerant to the presence of drug at the levels expected to be in some patents' serum at the time of sampling, leading to a reduced capability of detecting ADA. The development of more sensitive and drug tolerant assays for the detection of neutralizing antibodies to daclizumab would provide a more accurate measure and characterization of the patients' immune response to daclizumab.

PMCs are recommended to reassess specifications for (b) (4) charge variants after additional manufacturing experience is gained. Daclizumab drug substance and drug product release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. The specification for (b) (4) charge variants for both drug substance and drug product are based on process capability. Based on the statistical component, the limits should

be re-assessed when a sufficient number of marketed product lots have been released.

A PMC is recommended to establish a criteria for non-reduced CE-SDS for drug substance and drug product at release and on stability. The current daclizumab drug substance and drug product release and stability specifications do not include assessment of non-reduced CE-SDS for purity. The method was used during development and data suggest product related fragments do not change on stability and are generally low. However, data is limited and development of a release method and establishment of a corresponding specification is recommended. The sponsor will include a non-reduced CE-SDS method for information only until sufficient data is available to recommend an acceptance criteria.

A PMC is recommended to provide additional data to support the hold times to ensure that (b) (4) can be held without compromising the microbial quality of the product. This is appropriate for a PMC (b) (4)

However, supplemental data are needed (b) (4)  
The study will be conducted under a QA-approved protocol. The acceptance criteria of the protocol were provided in the BLA and were adequate.

A PMC is recommended to provide additional endotoxin recovery data. The spiking and hold study data from one drug product lot were provided and demonstrated adequate recovery of the spiked Control Standard Endotoxin (CSE) (b) (4). Data from two additional drug product lots are needed to confirm the validity of the endotoxin release tests for drug substance and drug product. In addition, the endotoxin spiking and hold study using one drug product lot showed endotoxin recoveries (b) (4)

The Agency recommended (b) (4)

This is appropriate for a PMC because the risk assessment for endotoxin control provided by the sponsor concluded minimum risk of endotoxin contamination (b) (4) of the drug substance manufacturing process and in the drug product manufacturing process. The endotoxin test (b) (4) has adequate endotoxin recovery. In addition, the endotoxin specifications for drug substance and drug product are (b) (4) lower than the safety threshold. The risk of endotoxin contamination above the safety threshold level is low.

## **B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

Below are the draft PMC/PMRs to be proposed to the sponsor should approvability be the recommendation.

- 1). Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against daclizumab in the presence of daclizumab levels that are expected to be present in samples at the time of patient sampling.
- 2). To re-evaluate the (b) (4) charge variant specification for drug substance after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.
- 3). To re-evaluate the (b) (4) charge variant specification for drug product after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.
- 4). To validate a non-reduced CE-SDS method and introduce the method into the drug substance and drug product specification. The analytical procedure, validation report, proposed specification acceptance criteria, and the data used to set the proposed acceptance criteria will be provided in the final study report.
- 5). Conduct microbial spiking studies (b) (4) product intermediates to demonstrate that the product intermediates do not support significant microbial growth under the proposed hold conditions.
- 6). Provide endotoxin recovery data from two additional drug product lots spiked with Control Standard Endotoxin (CSE).

## II. Summary of Quality Assessments

### A. CQA Identification, Risk and Lifecycle Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see [Appendix\\_A](#) for the Drug Substance and Drug Product Quality Review: OBP Assessment and [Appendix\\_B](#) Drug Substance Microbiology Review: Division of Microbiology Assessment.

Table 1: Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Origin	Control Strategy	Other
Potency	Efficacy	(b) (4)	Potency is tested at both release and on stability	N/A
ADCC	Efficacy	(b) (4)	(b) (4)	N/A
HMW Species	Efficacy and Immunogenicity			N/A
LMW Species	Efficacy			Non-reduced CE-SDS method available for characterization. Will become a specification test upon adequate data
Charge Variant Profile (b) (4)	Efficacy, Pharmacokinetics, and Potency			Specifications are based on process capability and a PMC is proposed to update limits as additional experience is

			(b) (4)	gained.
Endotoxin	Safety	(b) (4)	Monitored throughout process. Specification for release of (b) (4)	N/A

## **B. Drug Substance Daclizumab Quality Summary**

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to only drug substance. For additional information see [Appendix\\_A](#) for the Drug Substance and Drug Product Quality Review: OBP Assessment and [Appendix\\_B](#) Drug Substance Microbiology Review: Division of Microbiology Assessment.

CQA	Risk	Origin	Control Strategy	Other
Bioburden	Safety	(b) (4)	(b) (4) monitoring during process. Specification at release (b) (4)	N/A
(b) (4)	Safety and Immunogenicity	(b) (4)	(b) (4)	N/A
(b) (4)	Efficacy and Pharmacokinetics	(b) (4)	(b) (4)	N/A
(b) (4)	Safety	(b) (4)	(b) (4)	N/A
pH	Safety and Efficacy	(b) (4)	(b) (4) Testing of DS at release and on stability	N/A
(b) (4)	Safety and	(b) (4)	(b) (4)	N/A

	Immunogenicity	(b) (4)		
(b) (4)	Safety			N/A
Protein Content	Efficacy	(b) (4)		N/A
Appearance	Safety	(b) (4)		N/A
Identity	Safety and Efficacy	Not Applicable	(b) (4)	N/A
Osmolality	Safety	Controlled during formulation	Profile is sufficiently unique to discriminate	N/A
Polysorbate 80	Safety	(b) (4)		N/A



QUALITY ASSESSMENT BLA 761029 Daclizumab



Leachables	Safety		(b) (4) N/A
	Safety		N/A
	Safety		N/A

### 1. Description

Daclizumab is a humanized IgG1 antibody that was generated by standard monoclonal antibody techniques and is expressed in NS0 cells. (b) (4)

For additional information see Appendixes A and B of the initial integrated review memo.

### 2. Mechanism of action

Daclizumab is a humanized IgG1 monoclonal antibody that specifically binds to CD25, the alpha subunit of the human high-affinity interleukin-2 receptor. IL-2 receptor is a heterotrimeric protein expressed on the surface of certain immune cells, such as lymphocytes, that binds IL-2. The IL-2 receptor has contains multiple forms, generated by different combinations of three different protein components, often referred to as "chains": alpha (CD-25), beta (CD122), and gamma (CD132). The  $\alpha$  chain binds IL-2 with low affinity,  $\beta$  and  $\gamma$  together form a complex that binds IL-2 with intermediate affinity, primarily on memory T cells and NK cells; and all three receptor chains form a complex that binds IL-2 with high affinity on activated T cells and regulatory T cells. Daclizumab prevents binding of IL-2 to CD25, subsequently inhibits IL-2 signaling, including ILL-2 induced T cell proliferation and activated T cell responses. In addition, inhibition of IL-2 signaling by daclizumab also results in activation of immunoregulatory NK cells that gain access to the intrathecal compartment in multiple sclerosis and kill autologous activated T cells. For additional information see Appendix A of the initial integrated review memo.

### 3. Potency Assay

Daclizumab potency is assessed using a human T cell proliferation assay This assay evaluates the ability of daclizumab to inhibit IL-2-induced T cell proliferation The results, expressed in relative fluorescence units at (b) (4) nm, are plotted against the  $\log_{10}$  of sample concentration (b) (4) A (b) (4) analysis is used to estimate the inhibitory activity of daclizumab relative to reference standard (b) (4) Inhibition of IL-2-induced T cell proliferation is proportional to daclizumab concentration. For additional information see Appendix A of the initial integrated review memo.

### 4. Reference material(s)

A (b) (4) reference standard system was developed and is considered consistent with ICHQ6B recommendations. (b) (4)



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

CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety and Efficacy	[REDACTED]	(b) (4)	N/A
			Adequate container closure integrity Testing at release and stability	
Particulate Matter	Safety and Efficacy	[REDACTED]	(b) (4)	N/A
Appearance	Safety	[REDACTED]	Controlled during manufacture and tested for on release and stability	N/A
Protein Concentration	Efficacy	[REDACTED]	(b) (4) tested for on release and stability	N/A
Leachables	(b) (4)	[REDACTED]	(b) (4)	N/A



### **Summary of Drug Product Intended Use**

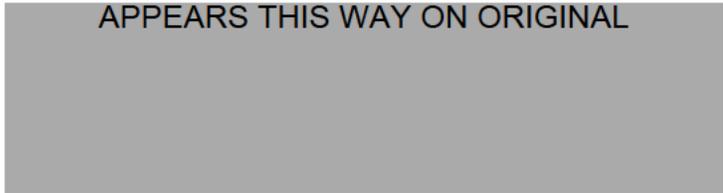
Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information on the characterization of ZINBRYTA see Appendix A for the Drug Substance and Drug Product Quality Technical Report: OBP Assessment and [Appendix C](#) Drug Product Microbiology Review: Division of Microbiology Assessment.

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

<b>CQA</b>	<b>Risk</b>	<b>Origin</b>	<b>Control Strategy</b>	<b>Other</b>
Sterility	Safety (infection)		(b) (4)	N/A
			Container closure integrity testing on stability.  Validation of shipping.  Sterility testing at release and on stability.	
Particulate Matter	Occlusion of blood vessels	(b) (4)	(b) (4)	
Appearance	Safety		Controlled during manufacture and tested for on release and stability	N/A
Identity	Safety and Efficacy	Not Applicable	(b) (4)  Profile is sufficiently	N/A

			unique to discriminate	
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APPEARS THIS WAY ON ORIGINAL



a. Potency and Strength

Potency is defined as the percent activity relative to the current daclizumab reference standard. The potency assay is the same as described in the DS section B3 of this memo. Daclizumab is available as a 150 mg/mL strength.

b. Summary of Product Design

Zinbryta will be available as a single pre-filled syringes with staked needles. The functionality and design of the pre-filled syringes (b) (4) was reviewed by CDRH. CDRH recommends approval.

c. Excipients

Excipients include sodium succinate anhydrous, succinic acid, sodium chloride, polysorbate 80, and water for injection. The excipients used in manufacturing are acceptable because they are compendial quality standard (b) (4)

The excipients are safe for use (b) (4)

For additional information see Appendix A of the initial integrated review memo.

d. Reference material(s)

There is no drug product specific reference material. The primary and working reference materials are drug substance. Please see drug substance reference materials for information.

e. Manufacturing Process

The manufacturing process for drug product (b) (4)

The control strategy includes (b) (4) critical and non-critical parameters and release testing of (b) (4) and the final drug product. Critical parameters selected for routine monitoring support (b) (4)

Process validation studies included manufacture of four commercial scale.

f. Container Closure System

The primary container closure system is a single use (b) (4) 1-mL syringe. Each syringe includes a 0.5 inch staked 29-gauge needle, a (b) (4) rubber plunger stopper, and rigid needle shield (b) (4)

g. Expiration Date & Storage Conditions

The sponsor conducted real time, accelerated, and stressed stability studies (b) (4) (b) (4) to support a dating period of 36 months when stored at 2-8°C. For further information see Appendix A of the initial integrated review memo and Appendix A of this memo.

h. List of co-packaged components N/A

## D. Novel Approaches

N/A

## E. Any Special Product Quality Labeling Recommendations

Store in a refrigerator at 2-8°C

Do not freeze

Protect from light

Room temperature storage allowed for up to 30 days

## F. Establishment Information

### G. Facilities

The subject BLA proposes manufacture of Daclizumab Drug Substance and Drug Product at the following facilities.

Biogen Idec, Inc. (b) (4) (FEI # (b) (4)) is responsible for DS manufacturing and (b) (4) release, and stability testing of the DS. It is also responsible for quality control testing of drug product. A Pre-Licensing Inspection (PLI) was conducted (b) (4). A four-item 483 was issued during with a recommendation of VAI. Release testing is also performed by Biogen Idec (b) (4) (FEI # (b) (4)).

The manufacturing of drug product, (b) (4) release, and stability testing is performed (b) (4) (FEI # (b) (4)). The PLI was waived on January 8, 2016.

The packaging of PFS is performed by (b) (4) (FEI # (b) (4)) and (b) (4) (FEI # (b) (4)).

The facility descriptions submitted in this BLA have been adequately described to support the approval of this submission.

For a complete summary see Appendix D: Drug Substance Facilities Review: Division of Inspectional Assessment.

## H. Lifecycle Knowledge Management

### a. Drug Substance

i. Protocols approved: annual stability protocol, qualification of new working reference standard, qualification of new working cell bank, (b) (4) protocol.

- ii. Outstanding review issues/residual risk - see sections 1A and 1B of this memo for post-marketing commitments.
- iii. Future inspection points to consider – (b) (4)

**b. Drug Product**

- i. Protocols approved: annual stability protocol
- ii. Outstanding review issues/residual risk – see sections 1A and 1B of this memo for post-marketing commitments.
- iii. Future inspection points to consider – none

**Quality Assessment Summary Tables**

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
<b>Product Type</b>				
1.	New Molecular Entity <sup>1</sup>	X	<input type="checkbox"/>	
2.	Botanical <sup>1</sup>	<input type="checkbox"/>	X	
3.	Naturally-derived Product	<input type="checkbox"/>	X	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	X	
5.	PET Drug	<input type="checkbox"/>	X	
6.	PEPFAR Drug	<input type="checkbox"/>	X	
7.	Sterile Drug Product	X	<input type="checkbox"/>	
8.	Transdermal <sup>1</sup>	<input type="checkbox"/>	X	
9.	Pediatric form/dose <sup>1</sup>	<input type="checkbox"/>	X	
10.	Locally acting drug <sup>1</sup>	<input type="checkbox"/>	X	
11.	Lyophilized product <sup>1</sup>	<input type="checkbox"/>	X	
12.	First generic <sup>1</sup>	<input type="checkbox"/>	X	
13.	Solid dispersion product <sup>1</sup>	<input type="checkbox"/>	X	
14.	Oral disintegrating tablet <sup>1</sup>	<input type="checkbox"/>	X	
15.	Modified release product <sup>1</sup>	<input type="checkbox"/>	X	
16.	Liposome product <sup>1</sup>	<input type="checkbox"/>	X	
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	X	
18.	Combination Product	X	<input type="checkbox"/>	Pre-filled syringe
19.	Other _____	X	<input type="checkbox"/>	Humanized Monoclonal Antibody

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
<b>Regulatory Considerations</b>				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Quality Considerations</b>				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.	Procedures and/or specifications	Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design <sup>1</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	



Appendix\_A for the Drug Substance and Drug Product Quality Review: OBP Assessment

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## 1. INSPECTIONAL ACTIVITIES

A pre-licensure inspection (PLI) of the drug substance manufacturing facility at Biogen, Inc. (b) (4) was conducted (b) (4) under FEI No. (b) (4). The inspection covered the manufacturing operations for daclizumab drug substance under BLA STN 761029. The inspection was conducted by reviewers in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of daclizumab. This PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. A four-item 483 was issued; (b) (4)

(u) (4)  
The initial recommendation of the inspection is voluntary action indicated (VAI). A waiver for the inspection of the drug product facility was completed on January 15, 2016.

## SUMMARY OF QUALITY ASSESSMENTS

### I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761029 for Zinbryta (daclizumab) manufactured by Biogen Idec, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Zinbryta (daclizumab) 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.

The Office of Biotechnology Products recommends approval of the proposed lot release/stability specifications and stability protocols for daclizumab drug substance and drug product.

The Office of Biotechnology Products recommends an expiry period of (b) (4) months for daclizumab drug substance when stored at (b) (4) °C and an expiry period of 36 months for daclizumab drug product when stored at 2-8°C.

### II. List Of Deficiencies To Be Communicated: None

### III. List Of Post-Marketing Commitments/Requirement:

As noted in the section describing the neutralization assay for anti-drug antibodies, poor drug tolerance is observed for the assay. A PMR is recommended. PMCs are recommended to reassess the specification for (b) (4) variants for both drug substance and drug upon obtaining additional manufacturing experience. A PMC is also recommended to establish a non-reduced CE-SDS method in the drug substance and drug product specification after collecting additional data.

### IV. Review Of Common Technical Document-Quality Module 1

#### A. Environmental Assessment Or Claim Of Categorical Exclusion

A claim for a categorical exclusion is being made under 21 CFR 25.31 (c) for substances that occur naturally in the environment. This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this

action would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the sponsor's knowledge, no extraordinary circumstances, as described in 21 CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This is appropriate.

#### V. Primary Container Labeling Review

The primary and secondary container labeling review was performed by Jibril Abdus-Samad, OBP.

#### VI. Review Of Common Technical Document-Quality Module 3.2

The document contains the review of the information provided on daclizumab drug substance (Section 3.2.S), drug product (Section 3.2.P), adventitious agents safety evaluation (3.2.A), and batch records (3.2.R).

#### Review of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assays are provided in the end of attachment A. The sponsor has developed immunoassays to detect binding antibodies to daclizumab (ADA) in human serum and a cell-based bioassay to determine the neutralizing potential of anti-drug antibodies (NAb). These assays have been used to evaluate the immunogenicity of daclizumab in clinical studies. A review of the ADA assay demonstrated it be sensitive, reproducible and sufficient for use in clinical studies. The review of the neutralizing assay demonstrated (b) (4)

A PMR is recommended to evaluate neutralizing response upon development of an improved assay.

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## DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

*Reviewer Note: All figures and tables are copied directly from the submission unless otherwise noted.*

### S. DRUG SUBSTANCE

#### 3.2.S.1.1 Nomenclature

Daclizumab is a humanized monoclonal antibody (IgG1) that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor.

##### USAN/INN Name

Daclizumab

##### CAS Number

152923-56-3

##### Biogen Idec Product Code

BIIB019

Biogen Idec Product Code for daclizumab produced at the (b) (4)

manufacturing facilities

BIIB019 (b) (4) (Drug Substance), BIIB019 (b) (4) (Drug Product)

Biogen Idec Product Code for daclizumab produced at the (b) (4)  
manufacturing facilities

BIIB019 (b) (4) (Drug Substance), BIIB019 (b) (4) (Drug Product)

Biogen Idec Product Code for DAC HYP produced at (b) (4)

manufacturing facilities

BIIB019 (b) (4) (Drug Substance), BIIB019 (b) (4) (Drug Product)

##### Synonyms

DAC HYP, Daclizumab HYP

#### 3.2.S.1.2 Structure

Daclizumab is a humanized IgG1 monoclonal antibody composed of two heavy chains and two identical kappa light chains with an approximate molecular weight of 144,000 dalton. The heavy chains and light chains consist of (b) (4)

(b) (4)

(b) (4)

Schematic diagrams of the sequence and structure of daclizumab below are copied directly from the submission.

(b) (4)

### Light Chain

(b) (4)

### Heavy Chain

### 3.2.S.1.3 General Properties

Daclizumab is a humanized IgG1 monoclonal antibody that specifically binds to CD25, the alpha subunit of the human high-affinity interleukin-2 receptor. IL-2 receptor is a heterotrimeric protein expressed on the surface of certain immune cells, such as lymphocytes, that binds IL-2. The IL-2 receptor contains multiple forms, generated by different combinations of three different protein components, often referred to as "chains": alpha (CD-25), beta (CD122), and gamma (CD132). The  $\alpha$  chain binds IL-2 with low affinity,  $\beta$  and  $\gamma$  together form a complex that binds IL-2 with intermediate affinity, primarily on memory T cells and NK cells; and all three receptor chains form a complex that binds IL-2 with high affinity on activated T cells and regulatory T cells. Daclizumab prevents binding of IL-2 to CD25, subsequently inhibits IL-2 signaling, including IL-2 induced T cell proliferation and activated T cell responses. In addition, inhibition of IL-2 signaling by daclizumab also results in activation of immunoregulatory NK cells that gain access to the intrathecal compartment in multiple sclerosis and kill autologous activated T cells. Daclizumab induces a low level of antibody dependent cell-mediated cytotoxicity, while complement dependent cytotoxicity activity is not observed.

The daclizumab drug substance is formulated as a colorless to slightly yellow, clear to slightly opalescent liquid at 150 mg/mL in (b) (4) sodium succinate, (b) (4) sodium chloride, (b) (4) polysorbate 80, pH 6.0. The isoelectric point is approximately (b) (4).

Potency is assessed using a human T cell proliferation assay. This assay evaluates the ability of daclizumab to inhibit IL-2-induced T cell proliferation. (b) (4)

(b) (4). Treatment with daclizumab prevents IL-2/CD25 binding and inhibits (b) (4) cell proliferation.

## P DRUG PRODUCT

### 3.2.P.1 Description and Composition of the Drug Product

Daclizumab drug product is a colorless to slightly yellow, clear to slightly opalescent liquid. It is free of visible particles and supplied in a 1-mL sterile Type 1 glass PFS and intended for subcutaneous administration. The drug product is stored at 5°C and sealed with a (b) (4) stopper.

**Table 1: Quantitative Composition of DAC HYP Drug Product**

Component	Function	Quality Standard	Nominal Amount per 150 mg/mL Dose (1.0 mL fill)
DAC HYP	Active Ingredient	Refer to Section 3.2.S.4.1; Specifications	150 mg
Sodium Succinate, Anhydrous	(b) (4)	Refer to Section 3.2.P.4.1; Specifications	5.94 mg
Succinic Acid		USP-NF	0.35 mg
Sodium Chloride		USP-NF/Ph.Eur./JP	5.84 mg
Polysorbate 80		USP-NF/Ph.Eur./JP	0.30 mg
Water For Injection		USP-NF/Ph.Eur./JP	(b) (4)
(b) (4)			

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

(b) (4)

The composition of the daclizumab formulation is provided in Table 1 below, copied directly from the submission.

**Table 1: Composition of DAC HYP Formulation**

Component	Nominal Amount per 150 mg/mL Dose (1.0 mL fill)
DAC HYP	150 mg
Sodium Succinate, Anhydrous	5.94 mg
Succinic Acid, USP-NF	0.35 mg
Sodium Chloride, USP-NF/Ph.Eur./JP	5.84 mg
Polysorbate 80, USP-NF/Ph.Eur./JP	0.30 mg
Water For Injection, USP-NF/Ph.Eur./JP	(b) (4)

#### 3.2.P.2.2 Drug Product

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Appendix\_B Drug Substance Microbiology Review: Division of Microbiology Assessment

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Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 2/3/2016  
**To:** Administrative File, STN 761029/0  
**From:** Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV  
**Endorsement:** Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV  
**Subject:** New Biologic License Applications (BLA)  
**Applicant:** Biogen Idec Inc.  
**US License:** 1697  
**Facility:** Biogen Idec Inc.  
[REDACTED] (b) (4)  
**FEI:** [REDACTED] (b) (4)  
**Product:** Zinbryta (daclizumab)  
**Dosage:** 150 mg/mL, 1 mL, solution for subcutaneous injection in pre-filled syringe  
**Indication:** Multiple sclerosis  
**PDUFA date:** May 27, 2016

---

**Recommendation:** The recommendation for approval of the drug substance part of this BLA from product quality microbiology perspective is pending until additional endotoxin spiking and hold study data have been submitted and reviewed.

---

### Review Summary

Biogen Idec has submitted this Biologics License Application (BLA) for daclizumab for the treatment of patients with relapsing multiple sclerosis. The drug substance (DS) is manufactured at the Biogen Idec facility [REDACTED] (b) (4). The drug product (DP) is manufactured [REDACTED] (b) (4) at the [REDACTED] (b) (4) site [REDACTED] (b) (4). The application contains CMC information in an eCTD format.

This review contains an assessment of the daclizumab drug substance section of the BLA from microbiology perspective.

### Assessment

#### **Drug Substance (3.2.S)**

##### **General Information (3.2.S.1)**

Daclizumab is a recombinant humanized IgG1 monoclonal antibody that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R) expressed on the surface of activated lymphocytes. Daclizumab High Yield Process (DAC HYP) modulates IL-2 signaling by blocking CD25-dependent, high-affinity IL-2 receptor signaling, but leaving intermediate-

affinity IL-2 receptor signaling intact. Daclizumab is expressed in an NS0 cell line. The drug substance contains 150 mg/mL daclizumab in (b) (4) mM sodium succinate, (b) (4) mM sodium chloride, (b) (4) % polysorbate 80, pH 6.0. (b) (4)

**Manufacture (3.2.S.2)**

**Manufacturer(s) (3.2.S.2.1)**

(b) (4)

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*Reviewer comment: Extractable and leachable evaluation should be reviewed by the OBP reviewer.*

*Satisfactory*

**Stability (3.2.S.7)**

A (b) (4)-month shelf-life has been proposed for the bulk drug substance. (b) (4)



*Reviewer comment: The stability program and data should be reviewed by the OBP reviewer.*

*Satisfactory*

**Conclusion**

- I. The recommendation for approval of the drug substance part of this BLA from product quality microbiology perspective is pending until additional endotoxin spiking and hold study data have been submitted and reviewed.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewers.
- III. See Panorama for compliance status of the facilities.

Cc: Chi  
Hughes  
Kelly

Primary reviewer signature

Secondary reviewer signature



Appendix\_C Drug Product Microbiology Review Division of Microbiology Assessment

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Process and Facilities  
Division of Microbiology Assessment

## PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**Reviewer:** Colleen Thomas, Ph.D.  
**Branch Chief:** Patricia Hughes, Ph.D.

BLA: 761029  
Applicant: Biogen  
US License Number: 1697  
Submission Reviewed: Original BLA  
Product: daclizumab (ZINBRYTA™)  
Indication: Multiple sclerosis  
Dosage Form: 150 mg/1 ml for subcutaneous injection  
DP Manufacturing Site: (b) (4)  
FDA Receipt Date: 27 February 2015  
Action Date: 28 December 2015

---

### Conclusion and Approvability Recommendation

The BLA was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval.

## Product Quality Microbiology Assessment: Drug Product

### Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	27 February 2015	Original BLA
0001	9 March 2015	Response to quality micro IR
0020	5 June 2015	Response to 74 Day Letter (quality micro IR)
0032	21 August 2015	Response to IR (DP testing site locations)
0037	25 September 2015	Response to quality micro IR
0062	2 March 2016	Response to quality micro IR
0064	7 March 2016	Response to quality micro IR
0069	21 March 2016	Response to quality micro IR
0075	13 April 2016	Response to quality micro IR

## Module 3.2

### P.1 Description and Composition of the Drug Product

The drug product (DP) is a sterile, preservative-free solution for subcutaneous injection supplied in single-use pre-filled syringes (PFS). The DP is stored at  $5 \pm 3^\circ\text{C}$ . The DP composition is shown in the table below, which was provided in section P.1.

**Table 1: Quantitative Composition of DAC HYP Drug Product**

Component	Function	Quality Standard	Nominal Amount per 150 mg/mL Dose (1.0 mL fill)
DAC HYP	Active Ingredient	Refer to <a href="#">Section 3.2.S.4.1; Specifications</a>	150 mg
Sodium Succinate, Anhydrous	(b) (4)	Refer to <a href="#">Section 3.2.P.4.1; Specifications</a>	5.94 mg
Succinic Acid	(b) (4)	USP-NF	0.35 mg
Sodium Chloride	(b) (4)	USP-NF/Ph.Eur./JP	5.84 mg
Polysorbate 80	(b) (4)	USP-NF/Ph.Eur./JP	0.30 mg
Water For Injection	(b) (4)	USP-NF/Ph.Eur./JP	(b) (4)

DESCRIPTION IS SATISFACTORY

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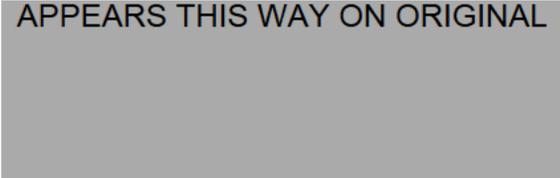
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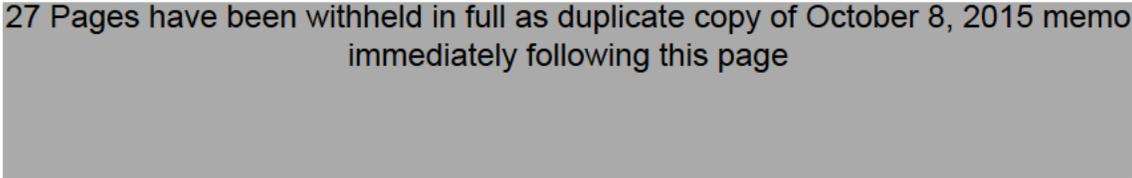


Appendix\_D Facilities Review: Division of Inspectional Assessment  
(Two reviews – dated October 8, 2015 and February 2, 2016)

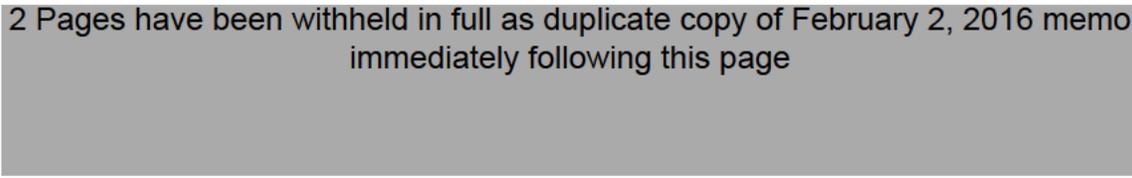
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2 Pages have been withheld in full as duplicate copy of February 2, 2016 memo immediately following this page





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Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg. 51, 10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 02/02/2016  
**To:** Administrative File, STN 761029/0  
**From:** Wayne Seifert, Consumer Safety Officer, CDER/OPQ/OPF/DIA  
**Endorsement:** Steven Fong, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DIA  
**Subject:** Original BLA  
**US License:** Pending  
**Applicant:** Biogen Inc.  
**Mfg Facility:** Drug Substance: Biogen, Inc., North Carolina (FEI (b)(4))  
Drug Product: (b)(4) (FEI (b)(4))  
**Product:** Zinbryta (Daclizumab)  
**Dosage:** Injection, Subcutaneous, 150 mg/1 ml  
**Indication:** Multiple Sclerosis  
**Due Date:** 02/27/2016

---

**RECOMMENDATION:** The application is recommended for approval from a facilities assessment standpoint.

---

## SUMMARY

This assessment is an addendum for a 10/08/2015 facilities review of BLA 761029/0. In the 10/08/2015 review, a final facilities recommendation was not made, because a compliance decision was still pending for the Biogen Inc. site (FEI (b)(4)) proposed for DS manufacture. A compliance decision of approve has now been rendered for the Biogen Inc. site. All listed facilities are now currently in a state of compliance and the application is recommended for approval from a facilities assessment standpoint.

## ASSESSMENT

An assessment of the proposed DS and DP manufacturing and testing sites for the subject BLA was presented in the 10/08/2015 facilities review. A final facilities recommendation was not rendered in that review, because of a post PAI compliance review for the proposed DS manufacturing Biogen, Inc. site FEI (b)(4) was not completed. The status of the Biogen Inc. DS site with respect to this application is now known and is summarized below:

- Biogen, Inc., (b)(4) On 11/04/2015, CDER/OPF/DIA rendered an approve decision for a PAI conducted (b)(4) to assess Zinbryta (Daclizumab) DS manufacture at this facility. This was a CPGM 7356.002M, ICH Q7A and CPGM 7346.832 based inspection that covered PAC code 46832M. Quality, Materials, Production, Laboratory Controls, Facilities, and Equipment Systems were assessed (b)(4) for Daclizumab DS manufacture.

## CONCLUSION

As amended, all manufacturing, packaging and testing sites listed in the submission are recommended for approval from a facilities assessment standpoint.

**Wayne E.  
Seifert -S**

Digitally signed by Wayne E. Seifert -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=20015932  
84, cn=Wayne E. Seifert -S  
Date: 2016.02.02 11:42:42 -05'00'

---

Wayne Seifert  
Consumer Safety Officer  
OPF Division of Inspectional Assessment  
Branch 1

**Steven Fong -S**

Digitally signed by Steven Fong -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
cn=Steven Fong -S, 0.9.2342.19200300.100.1.1=2000287453  
Date: 2016.02.02 09:36:48 -05'00'

---

Steven E. Fong, M.S., Ph.D.  
Microbiologist and Acting Quality Assessment Lead  
OPF Division of Inspectional Assessment  
Branch 1

**Determining When Pre-License / Pre-Approval Inspections are Necessary  
Inspection Waiver Memorandum**

**Date:** 01/15/2016  
**From:** Wayne Seifert, OPQ/OPF/DIA  
**To:** BLA File, STN 761029/0  
**Through:** Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1  
**Subject:** Inspection waiver memo for manufacture of Zinbryta DP (b) (4)

**Applicant:** Biogen Inc.

**Facility:** (b) (4)  
FEI # (b) (4)

**Product:** Zinbryta (Daclizumab) for Injection

**Dosage:** Injection, Subcutaneous, 150 mg/1 ml, Prefilled Syringe.

**Indication:** Multiple Sclerosis

**Waiver Recommendation**

Zinbryta DP will be manufactured at the (b) (4) facility (FEI (b) (4) (b) (4)). The proposed commercial manufacturing process for Zinbryta is (b) (4) PFS (b) (4). The facility was inspected by IOG from (b) (4) and classified VAI. CGMP coverage was provided for the (b) (4) profile during the inspection, and there were no concerns related to manufacture of PFS (b) (4) at the facility.

An inspection waiver for this site for the subject BLA is recommended based on the firm's compliance history, current GMP status, and current approval for manufacture of multiple (b) (4) products. (b) (4)

(b) (4) We recommend that inspection of the (b) (4) facility be waived for STN 761029/0.

## Summary

BLA STN 761029/0 was submitted by Biogen Inc., and Biogen provided information and data to support the manufacture of Zinbryta for injection, 150mg/ml. The manufacture of Zinbryta DS is performed at Biogen Inc. (b)(4) (FEI (b)(4)), and Zinbryta DP is manufactured at the (b)(4) facility (b)(4) (FEI (b)(4)). This waiver recommendation is in regards to Zinbryta DP manufacture at the (b)(4) facility.

## Facility Information

Zinbryta DP is manufactured (b)(4) (b)(4)

## Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

The (b)(4) site (b)(4) is currently approved for manufacture (b)(4)

2. *The previous inspection revealed significant GMP deficiencies in areas (b)(4)*

The previous inspections included Profile Class (b)(4) and were classified VAI or NAI.

3. *The establishment is performing significant manufacturing step(s) (b)(4)*

As noted in the response to Question 1, the (b)(4) manufacturing area is currently approved for manufacture (b)(4)

4. *The manufacturing process is sufficiently different* (b) (4)  
*from that of other approved products*  
*produced by the establishment.*

The proposed manufacturing scheme for Zinbryta is (b) (4)  
 at the (b) (4)  
 facility.

**Signed:**

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 Digitally signed by Wayne E. Seifert -S  
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 Wayne Seifert, DIA/OPF Reviewer

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 David Frucht, M.D. CONCUR DO NOT CONCURE  
 Acting Director, Division of Biotechnology Review and Research II  
 Office of Biotechnology Products, Office of Pharmaceutical Quality, CDER



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 08, 2015
To: Administrative File, STN 761029/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Steven Fong, Ph.D., CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 1697
Applicant: Biogen Inc.
Mfg Facility: Drug Substance: Biogen, Inc., (b)(4) (FEI (b)(4))
Drug Product: (b)(4) (FEI (b)(4))
Product: Zinbryta (Daclizumab)
Dosage: Injection, Subcutaneous, 150 mg/1 ml
Indication: Multiple Sclerosis
Due Date: February 27, 2016

RECOMMENDATION: As of 10/08/2015, the drug substance facility assessment is still pending for Biogen, Inc. FEI (b)(4) A Prior Approval Inspection was conducted (b)(4) with a compliance review pending. The inspection report and any applicable form responses will be reviewed before an overall recommendation can be made. The completed Overall Facility Assessment will be provided as an addendum to this review at a later date.

SUMMARY

The subject BLA proposes manufacture of Zinbryta (Daclizumab) DS at Biogen Inc. (b)(4) and Zinbryta DP (b)(4). Both are multi-product, contract manufacturing facilities. The final dosage form consists of PFS's containing 150 mg/mL Daclizumab API.

Zinbryta is a humanized monoclonal immunoglobulin gamma-1 antibody that binds CD25 and modulates IL-2 signaling. The Daclizumab DS manufacturing process consists of (b)(4)

The Daclizumab DP manufacturing process consists of (b)(4)

All facilities performing manufacturing, testing, and packaging of the DS and DP are acceptable or pending compliance review. The facility descriptions submitted for this BLA have been reviewed and found to be adequate to support the manufacturer of Daclizumab DS and DP.

**ASSESSMENT**

**3.2.S.2. DRUG SUBSTANCE FACILITIES**

The proposed Daclizumab DS Manufacturer, Master and Working Cell Bank Storage and Testing Facilities are listed in Table 1.

Table 1: DS Manufacturers for Daclizumab

Site Name	Address	FEI #	Responsibility
Biogen, Inc.	(b) (4)	(b) (4)	Master and Working Cell Bank Storage, Drug Substance Manufacturing, Drug Substance (b) (4) Testing and Drug Substance QC Testing.
Biogen, Inc.	14 Cambridge Center Cambridge, MA 02142	1220951	Working Cell Bank Manufacture, Master and Working Cell Bank Storage and Drug Substance (b) (4) Testing.
Biogen, Inc. (b) (4) Manufacturing	(b) (4)	(b) (4)	Drug Substance QC Testing (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4) Testing.
(b) (4)	(b) (4)	(b) (4)	(b) (4) Testing.

Taken from 0007 (8) 4/8/2015 Orig-1/Quality/Response to Information Request. All QC tests performed at the Biogen facilities (b) (4) and (b) (4) (b) (4) are identical and have been validated and/or qualified.

**Review Comment 1:** *The facilities for Manufacture, Master and Working Cell Bank Storage and Testing for Daclizumab DS are adequately described.*

• **Prior Inspection History for DS Manufacturing and Testing Sites**

- Biogen Inc. (FEI (b) (4)) – Drug Substance Facility

- Inspection Conducted (b) (4) by CDER/DIA/OBP. This was a PAI inspection for STN: 761029/0 (b) (4). A four item FDA Form was issued. **The inspection classification is pending.**
- Inspection Conducted (b) (4) by (b) (4)-DO. This was a surveillance inspection for the transfer of methods (b) (4). The inspection was classified NAI.
- Inspection Conducted (b) (4). This was a pre-licensed inspection of a biologic drug manufacturer. The inspection covered the Quality, Production, Material and Laboratory Control Systems. An FDA Form 483 was issued. The inspection was classified VAI.
- Inspection Conducted (b) (4). This was a pre-license Inspection. The inspection covered Quality, Production, Raw Materials, Facilities and Equipment and Laboratory Systems. A 3-item FDA Form 483 was issued. The inspection was classified VAI.
- Biogen Inc. (FEI 1220951) – Cell Bank Manufacture, Storage and Drug Substance (b) (4)  
(b) (4) Testing
  - Inspection Conducted (b) (4). This was a Surveillance inspection of a biologic drug substance manufacturer. The inspection covered Quality, Facilities and Equipment and Laboratory Control Systems. A 2-item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted (b) (4). This was an inspection of a pharmaceutical manufacturer. (b) (4)  
(b) (4)  
A 2-item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted from (b) (4). This was a pre-license inspection of the DS manufacturing site. The inspection covered DS manufacturing areas (b) (4).  
(b) (4) The inspection covered Quality, Production, Materials, Facilities and Equipment and Laboratories Systems. A three-item FDA Form 483 was issued. The inspection was classified VAI.
- Biogen Inc., (b) (4) (FEI (b) (4)) – Testing Facility
  - Inspection Conducted (b) (4). This was a surveillance inspection of a DS manufacturer. The inspection covered Quality, Production, Materials, and Laboratory Controls Systems, with limited coverage given to Facilities and Equipment and Packaging and Labeling Systems. A five-item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted (b) (4). This was a pre-license inspection of a DS manufacturing site. The inspection covered the (b) (4) facility for DS Manufacturing (b) (4).

- (b) (4)
- The inspection covered Quality, Production, Material, Facility and Equipment and Laboratory Systems. A three-item FDA Form 483 was issued. The inspection was classified VAI.
- Inspection Conducted (b) (4) This was a surveillance, GMP inspection of a Control Laboratory. The inspection covered Quality, Laboratory, and Packaging Systems. Limited coverage was also given to the Material System. This inspection was an initial inspection. The inspection was classified NAI.
  - (b) (4) (FEI (b) (4)) – Testing Facility
    - Inspection Conducted (b) (4) This was a comprehensive inspection. This was an initial (b) (4) inspection, with the previous FDA inspection conducted as a Drug GMP inspection (b) (4) The inspection was classified NAI.
  - (b) (4) (FEI (b) (4)) – Testing Facility
    - Inspection Conducted (b) (4) This was a CGMP inspection of a Contract Laboratory. The inspection covered Quality, Material, Facilities and Equipment and Laboratory Systems. The inspection was classified NAI.
    - Inspection Conducted (b) (4) This was for a licensed (b) (4) manufacturer. The inspection covered Quality and Production Systems. cursory coverage was given to the Laboratory System. A 3-item FDA Form 483 was issued. The inspection was classified VAI.
    - Inspection Conducted (b) (4) This was a cGMP inspection. The inspection covered Quality, Production, Facilities and Equipment, and Material Systems. An 8-item FDA Form 483 was issued. The inspection was classified VAI.

● **Current Prior Approval Inspection Decision**

- Biogen Inc. (FEI (b) (4)) – DS Facility  
Approved based on inspectional assessment.
- Biogen Inc. (FEI 1220951) – Cell Bank Manufacture, Storage and DS (b) (4) Testing  
Approved facility based on profile.
- Biogen Inc. (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on file review and District recommendation.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on file review and District recommendation.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on file review and District recommendation.

*Review Comment 2: The compliance status of facilities associated with the manufacture of Daclizumab DS is adequate.*

- **Remarks**

A summary of IR's and responses to them is presented below.

IR Submit Date	Receipt Date of Amendment Response	Amendment Supporting Number (SDN)	Amendment Sequence Number	Notes
4/1/2015	4/8/2015	0007	8	Testing at each location and clarification of validated methods.
08/13/2015	08/21/2015	0032	33	Life cycle approach to computer system validation. (b) (4) and routine testing (b) (4) (b) (4)

- **Overview of Daclizumab DS Manufacturing Operations Conducted** (b) (4)

Drug substance manufacture (b) (4)



8 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

### 3.2.A.1 DRUG PRODUCT FACILITIES

The proposed Daclizumab DP Manufacturer, Storage, Release and Stability Testing facilities for the Daclizumab DP are listed in Table 3.

Table 3: Facilities Proposed for Daclizumab DP Manufacturing and Testing\*

Site Name	Address	FEI #	Responsibility
[REDACTED]	[REDACTED]	(b) (4)	Drug Product Manufacturing, [REDACTED] Quality Control Testing and Visual Inspection.
			Visual Inspection.
			Quality Control Testing, [REDACTED] and Visual Inspection
			Quality Control Testing, [REDACTED] and Visual Inspection
			Visual Inspection.
Biogen, Inc.	5000 Davis Drive Research Triangle Park, NC 27709	(b) (4)	Quality Control Testing.
Biogen, Inc.	Biogen, Inc. (b) (4)	(b) (4)	Quality Control Testing and [REDACTED] Release.
[REDACTED]	[REDACTED]	(b) (4)	Secondary Packaging.
			Secondary Packaging.
			Stability Testing (Container Closure Integrity).

\*Taken from 0007 (8) 4/8/2015 Orig-1/Quality/Response to Information Request. All QC tests performed at the [REDACTED] facilities [REDACTED] are identical and have been validated and/or qualified. QC tests performed at the [REDACTED] sites [REDACTED] are identical and have been validated and/or qualified.

- **Prior Inspection History for DP Manufacturing and Testing Sites**

- [REDACTED] (FEI [REDACTED]) – Drug Product Manufacturer.

- Inspection Conducted [REDACTED] This was an inspection for a contract manufacturer [REDACTED] The inspection

covered Quality, Production and Packaging and Labeling System. An FDA Form 483 was issued. The inspection was classified VAI.

- Inspection Conducted (b) (4). This was a comprehensive (b) (4) (b) (4) Inspection. The inspection covered Quality, Materials, Facilities and Equipment, Production and Laboratory Control System. The inspection was classified NAI.

- Inspection Conducted (b) (4) This was a comprehensive inspection of a contract manufacturer (b) (4) The inspection was conducted at the (b) (4) facilit (b) (4) (b) (4) A one-item FDA Form 483 was issued. The inspection was classified VAI.

➤ (b) (4) (FEI (b) (4)) – Testing Facility.

- See (b) (4) FEI (b) (4) facility inspected during (b) (4) inspection.

➤ (b) (4) (FEI (b) (4)) – Testing Facility.

- Inspection Conducted (b) (4) This was an inspection (b) (4) (b) (4) The inspection covered Quality, Laboratory, and Production Systems. The inspection was classified NAI.

- Inspection Conducted (b) (4) This was for a (b) (4) (b) (4) contract manufacturer. The inspection covered Quality, Production, Laboratory, Materials, and part of the Facilities and Equipment System. The Packaging and Labeling System is not applicable to this site. The inspection was classified NAI.

- Inspection (b) (4) This was for a contract manufacturer of (b) (4) (b) (4) products. At least one deficiency (b) (4) (b) (4) was still present and has not been fully corrected and resulted in several FDA-483 citations of this facility during this inspection. The current inspection revealed additional deficiencies. The inspection was classified VAI.

➤ (b) (4) (FEI (b) (4)) – Testing Facility

- Inspection Conducted (b) (4) This was a GMP inspection of a (b) (4) (b) (4) manufacturer. The current inspection covered Quality, Production, Facilities and Equipment, and Laboratory Control Systems. A one-item FDA Form 483 was issued. The inspection was classified VAI.



- Biogen Inc. (b) (4) (FEI (b) (4)) – Testing Facility
  - Inspection Conducted (b) (4) This was a surveillance inspection of a DS manufacturer. The inspection covered Quality, Production, Materials, and Laboratory Controls Systems, with limited coverage given to Facilities and Equipment and Packaging and Labeling Systems. A five-item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted (b) (4) This was a pre-license inspection of a DS manufacturing site. The inspection covered the (b) (4) facility for DS manufacturing (b) (4). This was a first time FDA inspection of the (b) (4) facility at Biogen, (b) (4). The inspection covered Quality, Facility and Equipment, Production, Material, and Laboratory Systems. A three-item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted (b) (4) This was a surveillance, GMP inspection for a Control Testing Laboratory. The inspection covered Quality, Laboratory, and Packaging Systems. Limited coverage was also given to the Material System. This was a first time inspection for the site. The inspection was classified NAI.
- (b) (4) (FEI (b) (4)) – Testing Facility
  - Secondary packaging is of low significance from a GMP perspective. Therefore, and evaluation of this site is not required.
- (b) (4) (FEI (b) (4)) – Testing Facility
  - Secondary packaging is of low significance from a GMP perspective. Therefore, and evaluation of this site is not required.
- (b) (4) (FEI (b) (4)) – Testing Facility
  - Inspection Conducted (b) (4) This was an inspection of a contract laboratory and (b) (4) contract manufacturer. The inspections covered Quality, Facilities and Equipment and Laboratory Control Systems. An 8-Item FDA Form 483 was issued. The inspection was classified VAI.
  - Inspection Conducted (b) (4) This was a PAI inspection. The inspection covered Quality, Production, and Laboratory Systems. The inspection was classified NAI.
  - Inspection Conducted (b) (4) This was a Drug Manufacturing Inspections. The firm functions primarily as a Control Testing Laboratory, as a manufacturer (b) (4) as a contract manufacturer (b) (4). The inspection covered Quality, Production,

Facilities and Equipment and Laboratory Systems. The inspection was classified NAI.

• **Current Prior Approval Inspection Decisions**

- (b) (4) (FEI (b) (4)) – Drug Product Manufacture. Approved facility based on file review, District recommendation.
- (b) (4) FEI (b) (4) – Testing Facility  
See FEI (b) (4).
- (b) (4) FEI (b) (4) – Testing Facility  
Approved facility based on file review, District recommendation.
- (b) (4) (KG FEI (b) (4)) – Testing Facility  
Approved facility based on file review, District recommendation.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on profile.
- Biogen, Inc. FEI (b) (4) – Testing Facility  
Approve based on inspectional assessment.
- Biogen, Inc. (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on file review, District recommendation.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Secondary packaging is of low significance from a GMP perspective. Therefore, and evaluation of this site is not required.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Secondary packaging is of low significance from a GMP perspective. Therefore, and evaluation of this site is not required.
- (b) (4) (FEI (b) (4)) – Testing Facility  
Approved facility based on file review, District recommendation.

**Review Comment 16:** *The compliance status of facilities associated with the manufacture of Daclizumab DP is adequate.*

• **Remarks.**

Please refer to review page 5 for information requests submitted for this application and the SDN responses to them.

• **Overview of Daclizumab DP Manufacturing Operation Conducted**

(b) (4)

SOPs relevant to all computer systems include SOP 10649 - Definitions and Framework Conditions for Computer-Assisted Systems, SOP 10101 - Qualification of Suppliers, Contract Laboratories and Service Providers, SOP 10411 - Change Control System, SOP 11400 - Ongoing Operations, SOP 11394 - Security of Information Technology Systems, SOP 11395 - Procurement of IT Hardware and Software, SOP 11396 - Electronic Storage of Data and Software and Closing of IT Systems, SOP 11398 - Handling of Information-Technology Systems, SOP 11774 - New Acquisition and Change of Systems and SOP 11750 - Creation, Approval and Archiving of User Requirement Specification (URS) Documents for Primary Systems.

**Review Comment 22:** *Computer Systems and validation approach for computer systems used in Daclizumab DP manufacture appear adequate.*

## CONCLUSION

All proposed manufacturing and testing sites except for Biogen, Inc. (FEI (b) (4)) are recommended for approval from a facilities assessment standpoint. A final facilities recommendation for the BLA cannot be made until a compliance decision has been rendered for the (b) (4) PAI of Biogen, Inc. An Addendum stating the final OPF/DIA decisions for this site and the final facilities recommendation will be submitted to file once the final compliance decision is known.

Wayne E.  
Seifert -S

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Steven E. Fong, Ph.D.  
Microbiologist and Acting Quality Assessment Lead  
OPF Division of Inspection Assessment  
Branch 1

**Questions Presented in IR Submitted 4/21/2015**

1. For the facilities identified below, provide a summary of testing to be performed at each location. Additionally, clarify if they will use identical validated methods at each location specified.

a. Biogen Idec, Inc.

[Redacted] (b) (4)

Function: Drug Product QC Testing

FEI: [Redacted] (b) (4)

b. Biogen Idec

[Redacted] (b) (4)

Function: Drug Product QC Testing

FEI: [Redacted] (b) (4)

c.

[Redacted] (b) (4)

Function: Drug Product [Redacted] (b) (4) Testing

Drug Product QC Testing

FEI: [Redacted] (b) (4)

d.

[Redacted] (b) (4)

Drug Product QC Testing

FEI: [Redacted] (b) (4)

e.

[Redacted] (b) (4)

Function: Drug Product [Redacted] (b) (4) Testing

Drug Product QC Testing

FEI: [Redacted] (b) (4)

f. Biogen Idec, Inc.

[Redacted] (b) (4)

Function: Drug Substance [Redacted] (b) (4) Testing: Drug substance QC Testing

FEI: [Redacted] (b) (4)

g. Biogen Idec, Inc.

14 Cambridge  
Cambridge, MA

Function: Drug Substance [Redacted] (b) (4) Testing

FEI: 1220951

- h. Biogen Idec (b) (4)  
(b) (4)  
Function: Drug Substance QC Testing  
FEI: (b) (4)

2. From Module 1.1.2., FDA Form 356h Attachment, please correct the FEI number for the following facility:

- a. (b) (4)  
Function: DP Visual Inspection  
FEI: (b) (4)  
*FEI should be* (b) (4)

#### Questions Presented in IR Submitted 8/13/2015

**Question 16:** Regarding the Biogen Idec, Inc. site (FEI: (b) (4)) proposed for Daclizumab drug substance manufacture:

- Provide the lifecycle approach for computer system validation. Include the procedures for requalification and maintenance, and identify the computer systems and software used for cGMP activities.
- Identify the (b) (4) testing protocol for Daclizumab drug substance manufacture. For the testing protocol include the procedure, sampling point locations, and acceptance criteria.
- Provide an overview (b) (4). Include references to relevant SOPs.

**Question 17:** Regarding the (b) (4) site (FEI: (b) (4)) proposed for Daclizumab drug product manufacture:

- Provide the lifecycle approach for computer system validation. Include the procedures for requalification and maintenance, and identify the computer systems and software used for cGMP activities.
- Provide an overview for the requalification of manufacturing equipment and processes. Include references to relevant SOPs.