CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761244Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Assessment

Recommendation: Approval

BLA Number: 761244
Assessment Number: 1
Original Assessment Date: March 1, 2022
Date of Review Amendment; March 29, 2022

Drug Name/Dosage Form	Spevigo (spesolimab-sbzo)
Strength/Potency	60 mg/mL (450 mg/7.5 mL in a 10 mL vial)
Route of Administration	Intravenous (IV) use
Rx/OTC dispensed	Rx
Indication	Treatment of generalized pustular psoriasis (GPP)
Applicant/Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
US agent, if applicable	Not applicable

Product Overview:

Spevigo (spesolimab-sbzo) is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody that binds to the IL-36 receptor (IL-36R). Spesolimab binding to IL-36R prevents interaction with IL-36α, β, and γ, thereby inhibiting downstream signaling including pro-inflammatory and pro-fibrotic pathways. Spesolimab has mutations in the Fc region (L236A and L237A) to abrogate effector function activity. Spesolimab is indicated for the treatment of GPP, a severe skin and systemic condition marked by unpredictable acute flares that can be life-threatening. The finished drug product (DP) is a 60 mg/mL solution for infusion diluted with sodium chloride prior to administration. Each vial of spesolimab DP contains 450 mg (60 mg/mL) of spesolimab in (b) (4) of (b) (4) sodium acetate (b) (4) 2.4 mg (0.32 mg/mL) glacial acetic acid, 386 mg (51.4 mg/mL) sucrose, 39.5 mg (5.3 mg/mL) arginine hydrochloride, 3.0 mg (0.40 mg/mL) polysorbate 20, and water for injection. Each DP vial contains a total volume of 7.5 mL including overfill. The treatment regimen consists of a single 900 mg IV infusion over 90 minutes. If flare symptoms persist, an additional 900 mg may be administered a week after the initial dose.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Ian McWilliams	OPQ/OBP/DBRRII
Drug Product	Ian McWilliams	OPQ/OBP/DBRRII
Immunogenicity	Ian McWilliams	OPQ/OBP/DBRRII
Labeling	Vicky Borders Hemphill Ian McWilliams	OPQ/OBP OPQ/OBP/DBRRII
DS Micro and Facilities	Richard Ledwidge	OPQ/OPMA/DBM/BMB2
DP Micro and Facilities	Reyes Candau-Chacon	OPQ/OPMA/DBM/BMB2
RBPM	Nowrin Kakon	OPQ/OPRO
Team Lead	Brian Roelofs Madushini Dharmasena	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Jennifer Harmon	OND/DROII
Cross-disciplinary Team Lead	Amy Woitach	OND/OII/DDD
Medical Officer	Mary Kim/Amy Woitach	OND/OII/DDD
Pharmacology/Toxicology	Yongcheng Huang/Barbara Hill	OND/OII/DPTII
Clinical Pharmacology	Priya Brunsdon/Chinmay Shukla	OTS/OCP
Statistics	Matthew Guerra/Mohamed Alosh	OTS/OB/DBIII

1. Names:
   a. Proprietary Name: Spevigo
   b. Trade Name: Spevigo™ (spesolimab-sbzo) for intravenous use
   c. Non-Proprietary Name/USAN: spesolimab
   d. CAS Registry Number: 2097104-58-8
   e. INN Name: spesolimab
   f. OBP systematic name: MAB HUMANIZED (IGG1 FC) L234A, L235A ANTI Q9HB29 (ILRL2_HUMAN) [BI655130]
   g. Other name(s): BI 655130, 655130-01

Submissions Assessed:

Submission(s) Assessed	Document Date (disciplines affected)
eCTD 0001/SDN 1 – Original BLA Submission	10/01/2021 (OBP, OPMA)
eCTD 0004/SDN 4 – PQ IR 1 Response	11/10/2021 (OBP, OPMA)
eCTD 0005/SDN 5 – PQ IR 2 Response	11/12/2021 (OPMA)
eCTD 0007/SDN 8 – Amendment of Master Batch Records	11/23/2021 (OBP, OPMA)
eCTD 0009/SDN 9 – PQ IR 3 Response	12/8/2021 (OBP)
eCTD 00011/SDN 11 – PQ IR 5 Partial Response	12/29/2021 (OPMA)
eCTD 0012/SDN 12 – PQ IR 4 Response	01/03/2022 (OBP)
eCTD 0013/SDN 13 – PQ IR 5 Final Response and PQ IR 6 Response	01/10/2022 (OPMA)
eCTD 0015/SDN 15 – PQ IR 7 Response	01/31/2022 (OBP)
eCTD 0016/SDN 16 – PQ IR 8 Response	02/04/2022 (OPMA)
eCTD 0017/SDN 17 – PQ IR 9 and PQ IR 10 Responses	02/11/2022 (OBP, OPMA)
eCTD 0018/SDN 18 – PQ IR 11 Response	02/15/2022 (OPMA)
eCTD 0019/SDN 19 – PQ IR 12 Response	02/16/2022 (OPMA)
eCTD 0020/SDN 20 – PQ IR 13 Response	02/17/2022 (OPMA)
eCTD 0021/SDN 21 – PQ IR 14 Response	02/22/2022 (OPMA)
eCTD 0022/SDN 22 – PQ IR 14 Response	02/25/2022 (OPMA)
eCTD 0025/SDN 25 – PQ IR 6/8/11 Response	03/24/2022 (OPMA)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed
(b) (4)	III	(b) (4)		3	Adequate	N/A
	III			3	Adequate	N/A
	V			2	Adequate	April 26, 2021
	III			3	Adequate	N/A

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 assessed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	(b) (4)	Indication: ulcerative colitis; Parent IND for manufacturing information
IND	131311	Indication: GPP

3. Consults: None

4. Environmental Assessment

Boehringer Ingelheim is requesting categorical exclusion from preparing an Environmental Assessment on the basis of 21 CFR 25.31(b) for an action which does not increase the use of the active moiety, or if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761244 for Spevigo (spesolimab-sbzo) manufactured by Boehringer Ingelheim Pharmaceuticals, Inc.. The data submitted in this application are adequate to support the conclusion that the manufacture of Spevigo (spesolimab-sbzo) 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 the conditions specified in the package insert.

The final recommendation on approvability in the original OPQ Executive Summary Integrated Quality Assessment (IQA) completed and signed on March 1, 2022, was pending the submission of data supporting sterility assurance (b) (4) The Applicant provided data on March 24, 2022, to support sterility assurance (b) (4) The data were assessed by the Office of Pharmaceutical Manufacturing Assessment and found to be acceptable.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance and Drug Product:
    Boehringer Ingelheim Pharma GmbH & Co. KG
    Birkendorfer Strasse 65
    88397 Biberach an der Riss
    Germany
    FEI: 3002806518

- Fill size and dosage form: 450 mg in 7.5 mL (60 mg/mL) solution in a 10 mL vial for intravenous infusion

- Dating period:
  - Drug Product: 24 months at 2 to 8°C
  - Drug Substance: (b) (4) months at (b) (4)
  - Not Packaged
  - Stability Option:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes
  - Specified product
    - Spesolimab is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Spevigo (spesolimab) is an anti-IL-36 receptor (IL-36R) recombinant, humanized IgG1κ monoclonal antibody produced in the Chinese Hamster Ovary (CHO) (b) (4) cell line. IL-36 is a part of the IL-1 family of cytokines (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-37, and IL-38) and signals through unique heterodimeric receptor chains that are comprised of the cognate receptor protein and common IL-1 Receptor Accessory Protein (IL1RAP). IL-36R is also known as IL-1R6, Interleukin-1 receptor-like 2 (IL-1 RL2), and Interleukin-1 receptor-related protein 2 (IL-1 Rrp2). Interaction of spesolimab with the IL-36R blocks the pro-inflammatory cytokines IL-36α, IL-36β, and IL-36γ from binding cognate receptors and signaling through NFκB and MAP kinase pathways. Spesolimab is proposed for the treatment of GPP. Currently there are no FDA-approved treatments for GPP. Spesolimab has orphan drug designation and received a priority review designation for the treatment of GPP. Approval of spesolimab will address an unmet medical need for GPP.

Review of manufacturing has identified that the methodologies used for drug substance (DS) and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective pending the submission of the final data supporting sterility assurance of (b) (4) We also recommend approval of the commercial manufacture of spesolimab DS and DP at Boehringer Ingelheim Pharma GmbH & Co. KG (Biberach an der Riss, Germany) FEI: 3002806518. The OBP product quality and immunogenicity assay assessments, OPMA DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

There are no post-marketing commitments after the completion of the assessment from OPQ.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Identity	Efficacy and Safety	Intrinsic to the molecule	(b) (4)	The assay analysis includes visual comparison, identification of any new peaks with acceptance criteria, the comparison of retention time of five reference peaks in samples to RS chromatograms, and integration of relative peak areas for four of these peaks.
Potency (Inhibition of IL-36R binding)	Potency	Manufacturing process,		(b) (4) Potency was consistent through development and

		environmental stresses	(b) (4)	manufacturing processes were assessed to be comparable.
High molecular weight species (HMWS)	Potency, Safety (immunogenicity)	Manufacturing process, environmental stresses		Development data show that antibody oligomers that form HMWS have decreased potency.
Low molecular weight species (LMWS)	Efficacy	Manufacturing process, environmental stresses		Development data show the predominant LMWS (b) (4)
(b) (4) oxidation in CDR	Efficacy (Potency)	Primarily upstream manufacturing process		(b) (4)
(b) (4) oxidation in FcRn binding site	Pharmacokinetics	Upstream manufacturing process, environmental stresses		Potential impact on pharmacological activity (binding/potency) of fragments. Potential impact of fragments on clearance.
(b) (4) deamidation in CDR	Efficacy (potency)	Primarily upstream manufacturing process		(b) (4) Deamidation in CDR could impact target binding.
(b) (4)	Immunogenicity, safety	Primarily upstream manufacturing process		(b) (4)

(b) (4)	Pharmaco kinetics	Primarily upstream manufacturing process	(b) (4)	Potential impact of (b) (4) on clearance.

B. Drug Substance (spesolimab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance – clarity, color, and opalescence	Stability	Formulation components and stability	(b) (4)	N/A
Concentration	Efficacy	(b) (4) operations during DS manufacturing		N/A
Osmolality	Stability	Formulation		N/A
pH	Stability	Formulation		N/A
Host Cell Protein (Process Related Impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line		N/A
(b) (4)	Safety	Manufacturing process		N/A

			(b) (4)	
(b) (4)	Safety	Manufacturing Process		N/A
Culture medium and buffer components	Safety	Cell bank (b) (4)		Levels are below toxicological concern based on the risk assessment.
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials, manufacturing process.		N/A
Adventitious Agents (TSE, virus, mycoplasma)	Safety (systemic infection)	(b) (4) raw materials, cell bank, cell culture process		
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low because the DS is stored frozen and the primary product contact surface is stainless steel.

Elemental impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, (b) (4)	(b) (4)	N/A

- Description:
  Spevigo (spesolimab) is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody with an approximate molecular weight of 149 kilo Dalton after glycosylation. Spesolimab is produced using CHO cells (b) (4) Spesolimab has mutations in the Fc region (L236A and L237A) to abrogate effector function activity. Spesolimab is indicated for the treatment of GPP, a severe skin and systemic condition marked by unpredictable acute flares that can be life-threatening.

- Mechanism of Action (MoA):
  Spesolimab binds to IL-36R. Spesolimab binding to IL-36R prevents interaction with IL-36α, β, and γ, thereby inhibiting downstream signaling including pro-inflammatory and pro-fibrotic pathways.

- Potency Assay:
  The potency of spesolimab is assessed by a cell-based assay demonstrating binding to the target IL-36R. The assay principle is the induction of luciferase controlled by an NFκB response-element in a reporter gene cell line (NCI/LUC 130) by recombinant soluble IL-36. Binding is quantified by the inhibition of soluble recombinant IL-36 binding to IL-36R upon addition of spesolimab and reduction of luciferase signal. Potency is reported relative to the reference standard (RS) in each assay.

  Validation of the above potency assay was performed with RS and DS batches with the intended commercial formulation as well as stressed stability samples and foreign unspecific protein samples.

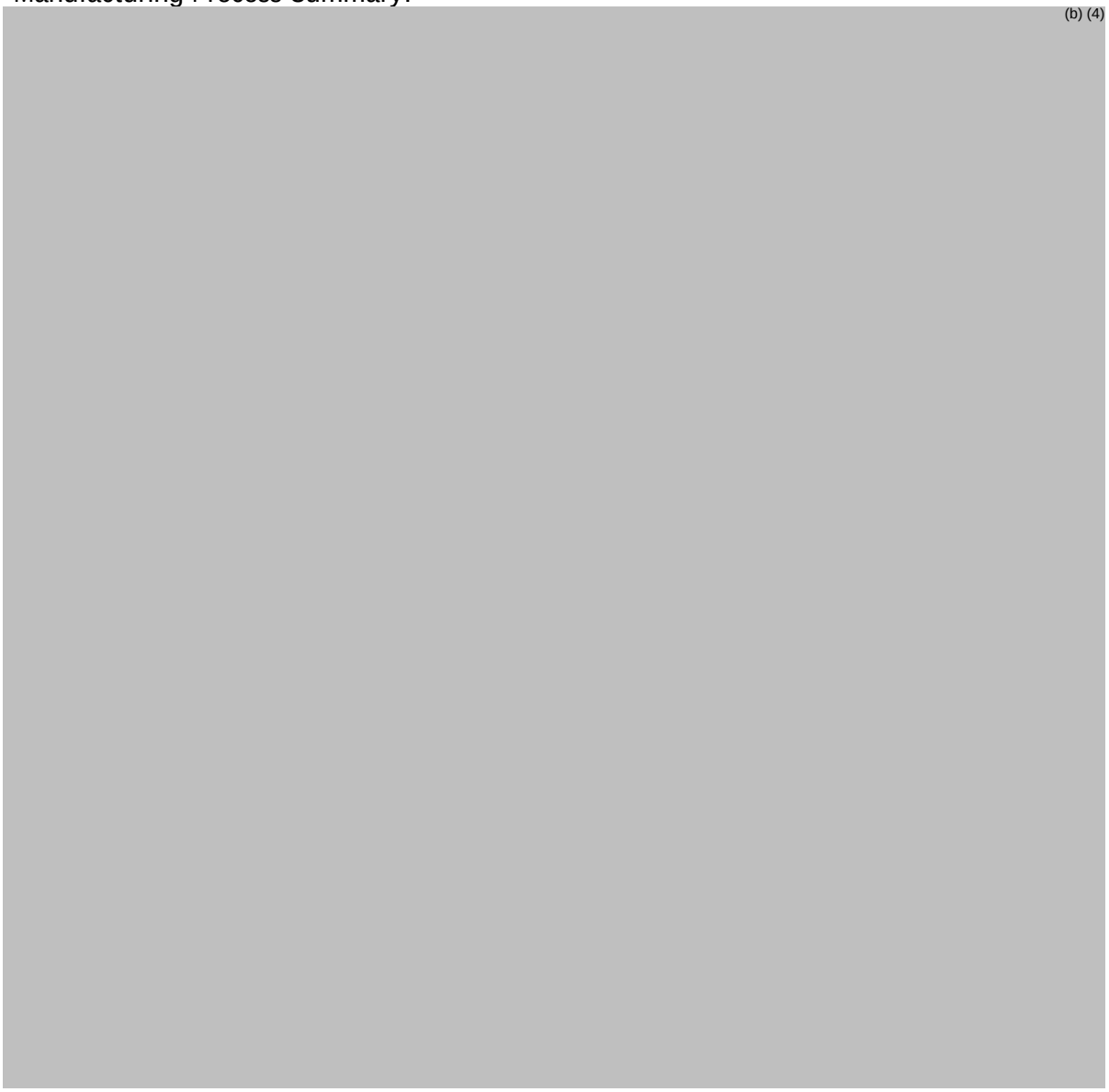
- Reference Materials:
  (b) (4)

- Critical Starting Materials or Intermediates:
  (b) (4)

(b) (4)

- Manufacturing Process Summary:

(b) (4)



- Container Closure:

(b) (4)

- Dating Period and Storage Conditions:

(b) (4)

C. Drug Product (spesolimab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Potency (Inhibition of IL-36R binding)	Potency	Manufacturing process, environmental stresses	(b) (4)	Refer to further description in CQA table above.
Appearance – Clarity, Opalescence, Color	Safety (immunogenicity), Stability	Manufacturing process, DS substance and (b) (4) during DP manufacturing		N/A
Osmolality and pH	Efficacy and stability	Formulation components and stability		N/A
Protein content	Efficacy	Manufacturing process including (b) (4)		N/A
Visible particles and sub-visible particles	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A

			(b) (4)	
High molecular weight species	Potency, Safety (immunogenicity)	Manufacturing process, DS substance and (b) (4) during DP manufacturing		Refer to further description in CQA table above.
Low molecular weight species (LMWS)	Efficacy	Manufacturing process, DS substance and (b) (4) during DP manufacturing		Refer to further description in CQA table above.
(b) (4) oxidation in CDR, (b) (4) oxidation in FcRn binding site	Efficacy	DS, manufacturing process		Refer to further description in CQA table above.
(b) (4) deamidation in CDR	Efficacy	DS, manufacturing process, potential impact (b) (4)		Refer to further description in DS CQA table above.
Endotoxins (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		N/A
Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Manufacturing process, failure of the container closure system		N/A
Polysorbate 20 content	Stability	Formulation components and stability		N/A
Extractable volume	Efficacy/Dosing	Fill process		N/A

			(b) (4)	
Container closure integrity (Sterility assurance)	Safety (maintenance of sterility during shelf-life or evaporation/leakage impacting concentration or content)	Container closure breaches during manufacture or storage		N/A
Elemental Impurities	Safety (Toxicity)	From product contact material during manufacturing and storage		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		The real-time study will be submitted as part of subsequent annual reports.

- Potency and Strength:
  Spesolimab is provided as 450 mg in 7.5 mL (60 mg/mL) (b) (4) Each DP vial contains a total volume of 7.5 mL including overfill. Potency is defined relative to the current spesolimab RS and assesses inhibition of IL-36 binding to IL-36R. The potency assay is the same as described in the DS section of this memo.

- Summary of Product Design:
  Spesolimab is supplied as 7.5 mL of 60 mg/mL solution for intravenous use. Sufficient overfill has been demonstrated to comply with USP<1151> recommendations. The minimum fill weight of (b) (4) g has been demonstrated to deliver sufficient volume (b) (4) mL) to account for residual DP after extraction and meet the extractable volume requirements.

- List of Excipients:
  The spesolimab DP excipients per 7.5 mL solution are (b) (4) sodium acetate (b) (4), 2.4 mg (0.32 mg/mL) glacial acetic acid, 386 mg (51.4 mg/mL) sucrose, 39.5 mg (5.3 mg/mL) arginine hydrochloride, 3.0 mg (0.40 mg/mL) polysorbate 20, and water for injection to a total volume of 7.5 mL.

- Reference Materials:
  The same RS are used for DS and DP.

- Manufacturing Process Summary:

(b) (4)

- Container Closure:
The primary container closure system for spesolimab DP consists of clear 10 mL (b) (4) glass vials with 20 mm grey (b) (4) rubber stoppers and aluminum crimp caps with a dark blue plastic button.

  Compatibility studies for spesolimab DP administration upon dilution to 3 or 12 mg/mL in various 100 mL isotonic saline infusion bags was demonstrated confirming the maintenance of product purity and protein content through the intended route of administration for intravenous infusion. An in-line 0.2 µm filter is used for administration.

- Dating Period and Storage Conditions:
The dating period for spesolimab DP is 24 months when stored at 2-8°C and protected from light. The in-use compatibility and stability data included in the BLA support the maintenance of product quality after preparation for infusion for up to 24 hours when stored at temperatures below 25°C. Microbial safety data were not provided to support storage after dilution to 24 hours, therefore, the recommended storage period for the spesolimab DP after preparation for administration is 4 hours at 2-8°C.

- Commercial Presentation:
The intended commercial presentation will be a single-dose vial containing 450 mg/7.5 mL (60 mg/mL) spesolimab as a clear to slightly opalescent and colorless to slightly brownish-yellow solution for intravenous use.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
- Store in a refrigerator at 2°C to 8°C
- Protect from light

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Substance Manufacturing Release and Stability Testing In Process Control Testing PRS Storage Site WRS Storage Site Cell Bank Manufacture Cell Bank Storage Cell Bank Testing Warehouse Storage of DS Intermediates and DS	Boehringer Ingelheim Pharma GmbH & Co. KG 88397 Biberach on der Riss, Germany	FEI: 3002806518 DUNS: 340700520	N/A	N/A	Approve – based on Waiver granted by OPMA/OBP
Cell Bank Safety Storage	Boehringer Ingelheim RCV GmbH & Co. KG 1121 Vienna, Austria	FEI: 3003433722 DUNS: 300010883	N/A	N/A	No Evaluation Necessary
Alternative Stability Testing WRS Storage	(b) (4)		N/A	N/A	Approve – Based on Previous History
Cell Bank Testing			N/A	N/A	No Evaluation Necessary
Cell Bank Testing			N/A	N/A	No Evaluation Necessary
Cell Bank Testing			N/A	N/A	No Evaluation Necessary

	(b) (4)				
Viral Clearance Study			N/A	N/A	No Evaluation Necessary
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Manufacturing Primary Packaging Release and Stability Testing In Process Control Testing Storage of Stability Samples Secondary Packaging and Labeling Warehouse Storage of DP Intermediates and DP (before & after release)	Boehringer Ingelheim Pharma GmbH & Co. KG 88397 Biberach on der Riss, Germany	FEI: 3002806518 DUNS: 340700520	N/A	N/A	Approve – based on Waiver granted by OPMA/OBP
Alternative Stability Testing Storage of Stability Samples	(b) (4)		N/A	N/A	Approve – Based on Previous History

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Boehringer Ingelheim Pharma GmbH & Co. KG (FEI: 3002806518) proposed for spesolimab DS and DP manufacturing. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage. This submission is recommended for approval from a facilities perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.3	(b) (4)		Annual Report
3.2.S.2.3			Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.5			Annual Report
3.2.S.7.2			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2	Leachables study	Real-time leachables study results.	Annual Report
3.2.P.8.2	DP stability updates	Annual stability results will be reported.	Annual Report
3.2.P.8.2	DP shelf-life extension	Primary stability batches, as well as PPQ batches, including PS20 testing by HPLC-CAD will be used to support potential shelf-life extension.	Annual Report

ii. Outstanding assessment issues/residual risk: None.

iii. Future inspection points to consider: None

Brian Roelofs

Digitally signed by Brian Roelofs
Date: 3/31/2022 03:12:19PM
GUID: 57f29d150070ca84f102970a51133e31

Madushini Dharmasena

Digitally signed by Madushini Dharmasena
Date: 3/31/2022 03:52:40PM
GUID: 5aecc01b00af3fb623ee1f6f17a576ea

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

/s/

BRIAN A ROELOFS
04/01/2022 12:46:34 PM
This addendum to the Executive Summary for BLA 761244 from OPQ contains the updated recommendation of approval and recommended language for the action letter.

Priority Assessment

Recommendation: Pending

BLA Number: 761244
Assessment Number: 1
Assessment Date: March 1, 2022

Drug Name/Dosage Form	Spevigo (spesolimab)
Strength/Potency	60 mg/mL (450 mg/7.5 mL in a 10 mL vial)
Route of Administration	Intravenous (IV) use
Rx/OTC dispensed	Rx
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Applicant/Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
US agent, if applicable	Not applicable

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Drug Product	Ian McWilliams	OPQ/OBP/DBRRII
Immunogenicity	Ian McWilliams	OPQ/OBP/DBRRII
Labeling	Vicky Borders Hemphill Ian McWilliams	OPQ/OBP OPQ/OBP/DBRRII
DS Micro and Facilities	Richard Ledwidge	OPQ/OPMA/DBM/BMB2
DP Micro and Facilities	Reyes Candau-Chacon	OPQ/OPMA/DBM/BMB2
RBPM	Nowrin Kakon	OPQ/OPRO
Team Lead	Brian Roelofs Madushini Dharmasena	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Jennifer Harmon	OND/DROII
Cross-disciplinary Team Lead	Amy Woitach	OND/OII/DDD
Medical Officer	Mary Kim/Amy Woitach	OND/OII/DDD
Pharmacology/Toxicology	Yongcheng Huang/Barbara Hill	OND/OII/DPTII
Clinical Pharmacology	Priya Brunsdon/Chinmay Shukla	OTS/OCP
Statistics	Matthew Guerra/Mohamed Alosh	OTS/OB/DBIII

1. Names:
   a. Proprietary Name: Spevigo
   b. Trade Name: Spevigo™ (spesolimab) for intravenous use
   c. Non-Proprietary Name/USAN: spesolimab
   d. CAS Registry Number: 2097104-58-8
   e. INN Name: spesolimab
   f. OBP systematic name: MAB HUMANIZED (IGG1 FC) L234A, L235A ANTI Q9HB29 (ILRL2_HUMAN) [BI655130]
   g. Other name(s): BI 655130, 655130-01

Submissions Assessed:

Submission(s) Assessed	Document Date (disciplines affected)
eCTD 0001/SDN 1 • •Original BLA Submission	10/01/2021 (OBP, OPMA)
eCTD 0004/SDN 4 • •PQ IR 1 Response	11/10/2021 (OBP, OPMA)
eCTD 0005/SDN 5 • •PQ IR 2 Response	11/12/2021 (OPMA)
eCTD 0007/SDN 8 • •Amendment of Master Batch Records	11/23/2021 (OBP, OPMA)
eCTD 0009/SDN 9 • •PQ IR 3 Response	12/8/2021 (OBP)
eCTD 00011/SDN 11 • •PQ IR 5 Partial Response	12/29/2021 (OPMA)
eCTD 0012/SDN 12 • •PQ IR 4 Response	01/03/2022 (OBP)
eCTD 0013/SDN 13 • •PQ IR 5 Final Response and PQ IR 6 Response	01/10/2022 (OPMA)
eCTD 0015/SDN 15 • •PQ IR 7 Response	01/31/2022 (OBP)
eCTD 0016/SDN 16 • •PQ IR 8 Response	02/04/2022 (OPMA)
eCTD 0017/SDN 17 • •PQ IR 9 and PQ IR 10 Responses	02/11/2022 (OBP, OPMA)
eCTD 0018/SDN 18 • •PQ IR 11 Response	02/15/2022 (OPMA)
eCTD 0019/SDN 19 • •PQ IR 12 Response	02/16/2022 (OPMA)
eCTD 0020/SDN 20 • •PQ IR 13 Response	02/17/2022 (OPMA)
eCTD 0021/SDN 21 • •PQ IR 14 Response	02/22/2022 (OPMA)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed
(b) (4)	III		(b) (4)	3	Adequate	N/A
	III			3	Adequate	N/A
	V			2	Adequate	April 26, 2021
	III			3	Adequate	N/A

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 assessed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	(b) (4)	Indication: ulcerative colitis; Parent IND for manufacturing information
IND	131311	Indication: GPP

3. Consults: None

4. Environmental Assessment

Boehringer Ingelheim is requesting categorical exclusion from preparing an Environmental Assessment on the basis of 21 CFR 25.31(b) for an action which does not increase the use of the active moiety, or if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on the approvability of STN 761244 for Spevigo (spesolimab) is pending the submission of data supporting sterility assurance (b) (4) The Applicant has provided preliminary data from one validation run to support sterility assurance (b) (4) s; results from the two remaining runs to be performed will be submitted before March 25th, 2022. A future addendum to this assessment memo will be submitted to document the outcome of the Office of Pharmaceutical Manufacturing Assessment (OPMA) assessment of this information.

From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER as well as OPMA, OPQ, CDER, do not note any other product quality deficiencies that would preclude approval of STN 761244 at this time.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance and Drug Product:
    Boehringer Ingelheim Pharma GmbH & Co. KG
    Birkendorfer Strasse 65
    88397 Biberach an der Riss
    Germany
    FEI: 3002806518

- Fill size and dosage form: 450 mg in 7.5 mL (60 mg/mL) solution in a 10 mL vial for intravenous infusion

- Dating period:
  - Drug Product: 24 months at 2 to 8°C
  - Drug Substance: (b) (4) months at (b) (4)
  - Not Packaged
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process validation drug substance batches and drug product lots.
    - For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes
  - Specified product
    - Spesolimab is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Spevigo (spesolimab) is an anti-IL-36 receptor (IL-[redacted] monoclonal antibody produced in the Chinese Hamster Ovary (CHO) (b) (4) cell line. IL-36 is a part of the IL-1 family of cytokines (IL-[redacted]18, IL-33, IL-[redacted]37, and IL-38) and signals through unique heterodimeric receptor chains that are comprised of the cognate receptor protein and common IL-1 Receptor Accessory Protein (IL1RAP). IL-36R is also known as IL-1R6, Interleukin-1 receptor-like 2 (IL-1 RL2), and Interleukin-1 receptor-related protein 2 (IL-1 Rrp2). Interaction of spesolimab with the IL-36R blocks the pro-inflammatory cytokines IL-[redacted] binding cognate receptors and signaling through [redacted] Currently there are no FDA-approved treatments for GPP. Spesolimab has orphan drug designation and received a priority review designation for the treatment of GPP. Approval of spesolimab will address an unmet medical need for GPP.

Review of manufacturing has identified that the methodologies used for drug substance (DS) and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective pending the submission of the final data supporting sterility assurance of (b) (4) We also recommend approval of the commercial manufacture of spesolimab DS and DP at Boehringer Ingelheim Pharma GmbH & Co. KG (Biberach an der Riss, Germany) FEI: 3002806518. The OBP product quality and immunogenicity assay assessments, OPMA DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

There are no PMCs at the time of this memorandum. [redacted] assessment of the information to be received March 25th, 2022, this memorandum will be amended.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Identity	Efficacy and Safety	Intrinsic to the molecule	(b) (4)	The assay analysis includes visual comparison, identification of any new peaks with acceptance criteria, the comparison of retention time of five reference peaks in samples to RS chromatograms, and integration of relative

				peak areas for four of these peaks.
Potency (Inhibition of IL-36R binding)	Potency	Manufacturing process, environmental stresses	(b) (4)	(b) (4) Potency was consistent through development and manufacturing processes were assessed to be comparable.
High molecular weight species (HMWS)	Potency, Safety (immunogenicity)	Manufacturing process, environmental stresses		Development data show that antibody oligomers that form HMWS have decreased potency.
Low molecular weight species (LMWS)	Efficacy	Manufacturing process, environmental stresses		Development data show the predominant LMWS (b) (4)
(b) (4) oxidation in CDR	Efficacy (Potency)	Primarily upstream manufacturing process		(b) (4)
(b) (4) oxidation in FcRn binding site	Pharmacokinetics	Upstream manufacturing process, environmental stresses		Potential impact on pharmacological activity (binding/potency) of fragments. Potential impact of fragments on clearance.
(b) (4) deamidation in CDR	Efficacy (potency)	Primarily upstream manufacturing process		(b) (4) Deamidation in CDR could impact target binding.
(b) (4)	Immunogenicity, safety	Primarily upstream manufacturing process		(b) (4)

			(b) (4)	not an endogenous human structure.
(b) (4)	Pharmaco kinetics	Primarily upstream manufacturing process		Potential impact of (b) (4) on clearance.

B. Drug Substance (spesolimab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Appearance •• clarity, color, and opalescence	Stability	Formulation components and stability	(b) (4)	N/A
Concentration	Efficacy	(b) (4) DS manufacturing		N/A
Osmolality	Stability	Formulation		N/A
pH	Stability	Formulation		N/A
Host Cell Protein (Process Related Impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line		N/A
(b) (4)	Safety	Manufacturing process		N/A

			(b) (4)	
(b) (4)	Safety	Manufacturing Process		N/A
Culture medium and buffer components	Safety	Cell bank (b) (4)		Levels are below toxicological concern based on the risk assessment.
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials, manufacturing process.		N/A
Adventitious Agents (TSE, virus, mycoplasma)	Safety (systemic infection)	(b) (4), raw materials, cell bank, cell culture process		
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low because the DS is stored frozen and the primary product contact surface is stainless steel.

			(b) (4)	
Elemental impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, (b) (4)		N/A

- Description:
  Spevigo (spesolimab) is a recombinant, humanized monoclonal immunoglobulin G1 (IgG1) antibody with an approximate molecular weight of 149 kilo Dalton after glycosylation. Spesolimab is produced using CHO cells (b) (4) Spesolimab has mutations in the Fc region (L236A and L237A) to abrogate effector function activity. Spesolimab is indicated for the treatment of GPP, a severe skin and systemic condition marked by unpredictable acute flares that can be life-threatening.

- Mechanism of Action (MoA):
  Spesolimab binds to IL-36R. Spesolimab binding to IL-36R prevents interaction with IL-36α, β, and γ, thereby inhibiting downstream signaling including pro-inflammatory and pro-fibrotic pathways.

- Potency Assay:
  The potency of spesolimab is assessed by a cell-based assay demonstrating binding to the target IL-36R. The assay principle is the induction of luciferase controlled by an NFκB response-element in a reporter gene cell line (NCI/LUC 130) by recombinant soluble IL-36. Binding is quantified by the inhibition of soluble recombinant IL-36 binding to IL-36R upon addition of spesolimab and reduction of luciferase signal. Potency is reported relative to the reference standard (RS) in each assay.

  Validation of the above potency assay was performed with RS and DS batches with the intended commercial formulation as well as stressed stability samples and foreign unspecific protein samples.

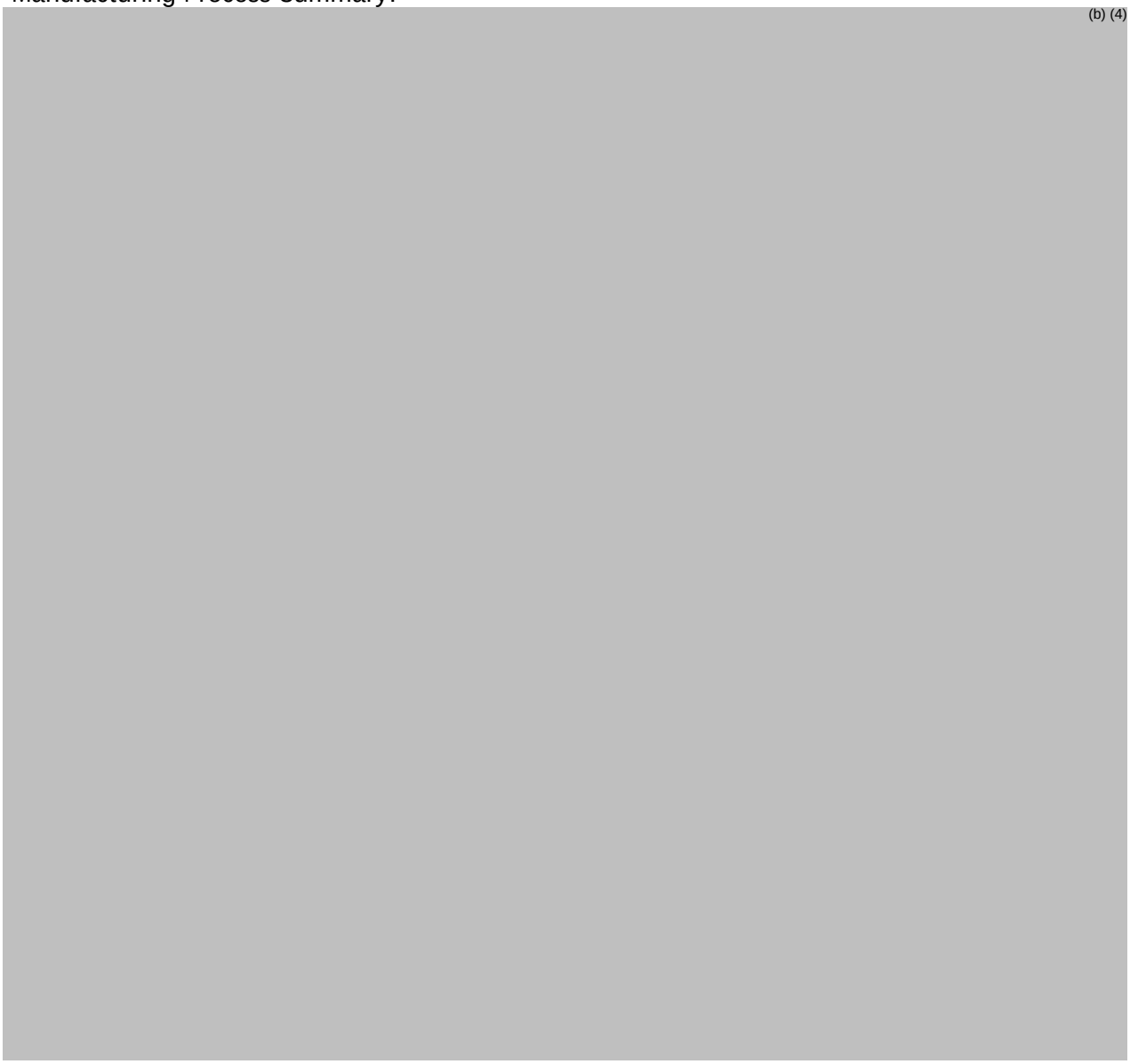
- Reference Materials:
  (b) (4)

- Critical Starting Materials or Intermediates:
  (b) (4)

(b) (4)

- Manufacturing Process Summary:

(b) (4)



- Container Closure:

(b) (4)

- Dating Period and Storage Conditions:

(b) (4)

C. Drug Product (spesolimab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Potency (Inhibition of IL-36R binding)	Potency	Manufacturing process, environmental stresses	(b) (4)	Refer to further description in CQA table above.
Appearance •• Clarity, Opalescence, Color	Safety (immunogenicity), Stability	Manufacturing process, DS substance and (b) (4) during DP manufacturing		N/A
Osmolality and pH	Efficacy and stability	Formulation components and stability		N/A
Protein content	Efficacy	Manufacturing process including (b) (4)		N/A
Visible particles and sub-visible particles	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles		N/A

		could be product or foreign particles	(b) (4)	
High molecular weight species	Potency, Safety (immunogenicity)	Manufacturing process, DS substance and (b) (4) during DP manufacturing		Refer to further description in CQA table above.
Low molecular weight species	Efficacy	Manufacturing process, DS substance and (b) (4) during DP manufacturing		Refer to further description in CQA table above.
(b) (4) oxidation in CDR, (b) (4) oxidation in FcRn binding site	Efficacy	DS, manufacturing process		Refer to further description in CQA table above.
(b) (4) deamidation in CDR	Efficacy	DS, manufacturing process, potential impact (b) (4)		Refer to further description in DS CQA table above.
Endotoxins (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		N/A
Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Manufacturing process, failure of the container closure system		N/A
Polysorbate 20 content	Stability	Formulation components and stability		N/A
Extractable volume	Efficacy/Dosing	Fill process		N/A

			(b) (4)	
Container closure integrity (Sterility assurance)	Safety (maintenance of sterility during shelf-life or evaporation/leakage impacting concentration or content)	Container closure breaches during manufacture or storage		N/A
Elemental Impurities	Safety (Toxicity)	From product contact material during manufacturing and storage		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		The real-time study will be submitted as part of subsequent annual reports.

- Potency and Strength:
  Spesolimab is provided as 450 mg in 7.5 mL (60 mg/mL) in (b) (4) Each DP vial contains a total volume of 7.5 mL including overfill. Potency is defined relative to the current spesolimab RS and assesses inhibition of IL-36 binding to IL-36R. The potency assay is the same as described in the DS section of this memo.

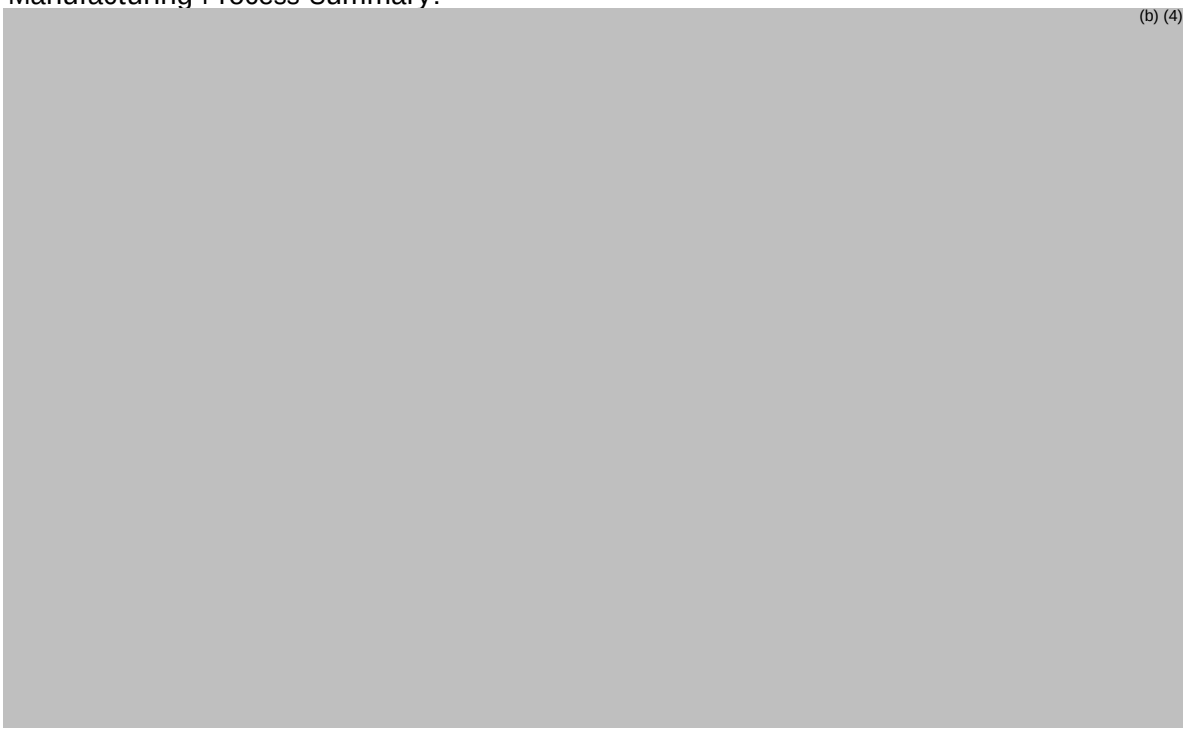
- Summary of Product Design:
  Spesolimab is supplied as 7.5 mL of 60 mg/mL solution for intravenous use. Sufficient overfill has been demonstrated to comply with USP<1151> recommendations. The minimum fill weight of (b) (4) g has been demonstrated to deliver sufficient volume (b) (4) mL) to account for residual DP after extraction and meet the extractable volume requirements.

- List of Excipients:
  The spesolimab DP excipients per 7.5 mL solution are (b) (4) sodium acetate (b) (4), 2.4 mg (0.32 mg/mL) glacial acetic acid, 386 mg (51.4 mg/mL) sucrose, 39.5 mg (5.3 mg/mL) arginine hydrochloride, 3.0 mg (0.40 mg/mL) polysorbate 20, and water for injection to a total volume of 7.5 mL.

- Reference Materials:
  The same RS are used for DS and DP.

- Manufacturing Process Summary:

(b) (4)



- Container Closure:
  The primary container closure system for spesolimab DP consists of clear 10 mL (b) (4) glass vials with 20 mm grey (b) (4) rubber stoppers and aluminum crimp caps with a dark blue plastic button.

  Compatibility studies for spesolimab DP administration upon dilution to 3 or 12 mg/mL in various 100 mL isotonic saline infusion bags was demonstrated confirming the maintenance of product purity and protein content through the intended route of administration for intravenous infusion. An in-line 0.2 µm filter is used for administration.

- Dating Period and Storage Conditions:
  The dating period for spesolimab DP is 24 months when stored at 2-8°C and protected from light. The in-use compatibility and stability data included in the BLA support the maintenance of product quality after preparation for infusion for up to 24 hours when stored at temperatures below 25°C. Microbial safety data were not provided to support storage after dilution to 24 hours, therefore, the recommended storage period for the spesolimab DP after preparation for administration is 4 hours at 2-8˚C.

- Commercial Presentation:
  The intended commercial presentation will be a single-dose vial containing 450 mg/7.5 mL (60 mg/mL) spesolimab as a clear to slightly opalescent and colorless to slightly brownish-yellow solution for intravenous use.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2°C to 8°C
- Protect from light

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Substance Manufacturing Release and Stability Testing In Process Control Testing PRS Storage Site WRS Storage Site Cell Bank Manufacture Cell Bank Storage Cell Bank Testing Warehouse Storage of DS Intermediates and DS	Boehringer Ingelheim Pharma GmbH & Co. KG 88397 Biberach on der Riss, Germany	FEI: 3002806518 DUNS: 340700520	N/A	N/A	Approve • •based on Waiver granted by OPMA/OBP
Cell Bank Safety Storage	Boehringer Ingelheim RCV GmbH & Co. KG 1121 Vienna, Austria	FEI: 3003433722 DUNS: 300010883	N/A	N/A	No Evaluation Necessary
Alternative Stability Testing WRS Storage	(b) (4)		N/A	N/A	Approve • •Based on Previous History
Cell Bank Testing			N/A	N/A	No Evaluation Necessary
Cell Bank Testing			N/A	N/A	No Evaluation Necessary
Cell Bank Testing			N/A	N/A	No Evaluation Necessary

	(b) (4)				
Viral Clearance Study			N/A	N/A	No Evaluation Necessary
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug Product Manufacturing Primary Packaging Release and Stability Testing In Process Control Testing Storage of Stability Samples Secondary Packaging and Labeling Warehouse Storage of DP Intermediates and DP (before & after release)	Boehringer Ingelheim Pharma GmbH & Co. KG 88397 Biberach on der Riss, Germany	FEI: 3002806518 DUNS: 340700520	N/A	N/A	Approve • •based on Waiver granted by OPMA/OBP
Alternative Stability Testing Storage of Stability Samples	(b) (4)		N/A	N/A	Approve • •Based on Previous History

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Boehringer Ingelheim Pharma GmbH & Co. KG (FEI: 3002806518) proposed for spesolimab DS and DP manufacturing. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspection coverage. This submission is recommended for approval from a facilities perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.3	(b) (4)		Annual Report
3.2.S.2.3			Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.2.5			Annual Report
3.2.S.5			Annual Report
3.2.S.7.2			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report
3.2.R			Annual Report

ii. Outstanding assessment issues/residual risk: None

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2	Leachables study	Real-time leachables study results.	Annual Report
3.2.P.8.2	DP stability updates	Annual stability results will be reported.	Annual Report
3.2.P.8.2	DP shelf-life extension	Primary stability batches, as well as PPQ batches, including PS20 testing by HPLC-CAD will be used to support potential shelf-life extension.	Annual Report

ii. Outstanding assessment issues/residual risk: The Applicant has committed to provide data supporting the validation (b) (4) by March 25th. Additional data (b) (4) will also be provided.

iii. Future inspection points to consider: None

Brian Roelofs

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

/s/

BRIAN A ROELOFS
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