

CHECK LIST FOR BATCH RELEASE OF MARKETED BIOLOGICAL PRODUCTS

Company: Celltrion Inc.

Product trade name: Denosumab (CT-P41) Drug Substance

Batch number: 22200P006

MANUFACTURER AND PRODUCT FILE

	✓	N/A
Master Cell Bank and Working Cell Bank <i>Company & Address (activity):</i> BioReliance Ltd. , Todd Campus, West of Scotland Science Park Acre Road, Glasgow , G20 0XA, UK (Production and testing of MCB and WCB). BioReliance Ltd. , Hillfoots Road, Stirling University Innovation Park, Stirling , FK9 4NF, UK (Storage of MCB and WCB) BioReliance Ltd. , Pentlands Science Park, Bush Loan, Penicuik, Midlothian, EH26 0PZ, UK (Testing MCB and WCB) WuXi Advanced Therapies, Inc. , 400 Rouse Boulevard, Philadelphia, PA, 19112, United States (Testing of CT-P41 unprocessed bulk)		☐ N/A
➤ cGMP certificates (<i>Certificate reference and inspection date</i>): BioReliance Ltd. – Glasgow - Local: MHRA Certificate No: UK MIA 22774 Insp GMP 13987/4473-0031. Inspection date: 13.02.2025 - EU: Not available - FDA: Not available BioReliance Ltd – Stirling - Local: MHRA Certificate No: UK GMP 22774 Insp GMP/IMP 22774/31007-0023. Inspection date: 02.05.2025 - EU: Not available - FDA: Not available BioReliance Ltd – Pentlands - Local: MHRA Certificate No: UK GMP 22774 Insp GMP/IMP 22774/2062763-0012 [H]. Inspection date: 19.03.2025 (Desk-based assessment of GMPs). - EU: Not available - FDA: Not available WuXi Advanced Therapies, Inc - Local: Not available, requested. - EU: Certificate issued by Netherlands Health Agency. Certificate number NL/H 24/2053682 and inspection date 10.07.2024. - FDA: No recent inspection evidence available.	✓	

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	✓	N/A
➤ GMP audits (full audit report, CAPA plan updated, CV of the auditor are to be available) (<i>Audit report reference and audit date</i>) • BioReliance Ltd. – Glasgow & BioReliance Ltd – Stirling & BioReliance Ltd – Pentlands: Nuvisan Audit on 12-13.07.2022 (Remote audit). <i>According to Celltrion's confirmation, the audit re-evaluation cycle for BioReliance Ltd was extended to four years based on their internal risk assessment. However, based on the recommendation of another Qualified Person (QP), next audit is scheduled for August 2025. When available, the audit report will be shared with Kymos.</i> • WuXi Advanced Therapies, Inc: Celltrion audit 22-23.10.2024 (On-site audit). General audit QC Testing, Unprocessed bulk testing, cell bank testing.	✓	
➤ Current dossier sections of 3.2.S. provided	✓	
Drug Substance Manufacturer/s ☐ N/A <i>Company & Address (activity):</i> Celltrion, Inc. Plant II (CLT2) 20, Academy-ro 51 Beon-Gil, Yeonsu-gu, Incheon, 22014, Republic of Korea (Production, release testing, stability testing, storage of MCB and WCB and testing the WCB)		
➤ cGMP certificates (<i>Certificate reference and inspection date</i>): ○ Local: GMP certificate requested. Manufacturing license 2569. ○ EU: SE-H-GMP-24-073864 issued by Sweeden Authorities, inspection date 31.05.2024 ○ FDA: Requested	✓	
➤ GMP audits (full audit report, CAPA plan updated, CV of the auditor are to be available) (<i>Audit report reference and audit date</i>) <i>Audit Report A/25.003 Nuvisan, conducted 01-03.04.2025</i>	✓	
➤ Annual PQR reports received and reviewed <i>n/a as it is new product to be released in 2025</i>		✓
➤ On-Going Stabilities results updated and reviewed. All results are within the registered specifications (at least 1 batch/dose/year) <i>DS batches manufactured in 2022 on-going stability up to 24 months.</i>	✓	
➤ Current dossier sections of 3.2.S. provided	✓	
Finished Product Manufacturer/s ☒ N/A <i>Company & Address (activity):</i>		
➤ cGMP certificates (<i>Certificate reference and inspection date</i>): ○ Local:		

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	✓	N/A
○ EU: ○ FDA:		
➤ GMP audits (full audit report, CAPA plan updated, CV of the auditor are to be available) (<i>Audit report reference and audit date</i>)		
➤ Periodic Aseptic Process Simulation Report provided and reviewed (for sterile products) (<i>Audit report reference and issuance date</i>)		
➤ Annual PQR reports received and reviewed		
➤ On-Going Stabilities results updated and reviewed. All results are within the registered specifications (at least 1 batch/dose/year)		
➤ Quality Technical Agreement in place		
➤ Current dossier sections of 3.2.P. provided		
Subcontractors		☒ N/A
<i>Company & Address (activity):</i> See MCB & WCB involved sites.		
➤ Warehouse (<i>Quality Certificates, inspection date</i>): ○ GMP: ○ GDP: ○ WDA: ○ GMP Audits (full audit report, CAPA plan updated, CV of the auditor are to be available) (<i>Audit report reference and audit date</i>)		
➤ Others <i>Company & Address (activity):</i> ○ Quality Certificates (<i>Certificate reference and inspection date</i>): ○ GMP Audits (full audit report, CAPA plan updated, CV of the auditor available) (<i>Audit report reference and audit date</i>)		

BATCH RECORDS REVIEW

	✓	N/A
Batch manufacturing record of Master Cell Bank		☒ N/A
➤ Master cell bank batch identification (if available) Information not available		

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	✓	N/A																
Batch manufacturing record of Working Cell Bank	☐	N/A																
➤ Working cell bank batch identification Batch 1558.01	✓																	
➤ Batch manufacturing records edition Documentation not available		✓																
➤ Vial identification Vial number 172		✓																
➤ CoA (certificate of analysis) or equivalent document GMP Certificate Compliance review. CoA with no number (Batch 1558.01 and Study AF75VF.912000.BUK)	✓																	
➤ Deviations and CAPA registered, and deviation reports provided. They are reviewed and accepted. Summary of deviation in Study AF75VF.912000.BUK <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr> <th style="width: 15%;">Date Raised</th> <th style="width: 15%;">Deviation</th> <th style="width: 45%;">Description</th> <th style="width: 25%;">Impact Assessment</th> </tr> </thead> <tbody> <tr> <td>09.09.2019</td> <td>377302</td> <td>Pre-released of 1 vial of 1557.01 MCB for use in the manufacture of 1558.01 WCB.</td> <td>Minor</td> </tr> <tr> <td>27.09.2019</td> <td>379795</td> <td>Operator did not clean BSC visor as per SOP KPMP1092</td> <td>Minor</td> </tr> <tr> <td>03.10.2019</td> <td>380563</td> <td>Shake bases within Incubators in Lab2 not running.</td> <td>Minor</td> </tr> </tbody> </table>	Date Raised	Deviation	Description	Impact Assessment	09.09.2019	377302	Pre-released of 1 vial of 1557.01 MCB for use in the manufacture of 1558.01 WCB.	Minor	27.09.2019	379795	Operator did not clean BSC visor as per SOP KPMP1092	Minor	03.10.2019	380563	Shake bases within Incubators in Lab2 not running.	Minor	✓	
Date Raised	Deviation	Description	Impact Assessment															
09.09.2019	377302	Pre-released of 1 vial of 1557.01 MCB for use in the manufacture of 1558.01 WCB.	Minor															
27.09.2019	379795	Operator did not clean BSC visor as per SOP KPMP1092	Minor															
03.10.2019	380563	Shake bases within Incubators in Lab2 not running.	Minor															
➤ Master batch record of the BMR approved Documentation not available		✓																
Batch manufacturing record of Drug substance	☐	N/A																
➤ Drug Substance batch identification Omalizumab Drug Substance batch 22200P006	✓																	
➤ Batch manufacturing record edition and approval for Upstream and Downstream process. 200P-0001 v3.0 - Cell Expansion in Shake Flasks 200P-0002 v2.0 - Cell Expansion in 120 L Bioreactor(s) 200P-0003 v2.0 - Cell Expansion in 600 L Bioreactor(s) 200P-0004 v2.0 - Cell Expansion in 4500 L Bioreactor(s) 200P-0005 v2.0 - Cell Expansion in 15000 L Bioreactor(s) 200P-0006 v4.0 - Harvest and Recovery 200P-0007 v4.0 - Initial Purification 100M-0008 v4.0 - Final Purification	✓																	

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	✓	N/A
➤ In the Batch Record and supporting documentation, the raw data is recorded according to Good Documentation Practices	✓	
➤ All attachments (if any) to the Batch Manufacturing Record are received and reviewed. Ensure that critical records for sterile production are available, reviewed, and show results within the approved specifications/parameters: ○ Filling of DS: Filter integrity tests results pre and post product filtration within the acceptance criteria ☒	✓	
➤ The Batch Record includes the registry and approval of starting materials/auxiliary solutions, and they are within the validity period.	✓	
➤ The Batch Record includes the registry of equipment, calibration/qualification status and cleaning status (attached status labels if necessary). All are within validity period.	✓	
➤ The Batch Record properly documents line clearance.	✓	
➤ All registered in-process controls are appropriately carried out and comply with the acceptance criteria defined in the CTD (3.2.S).	✓	
➤ Environmental controls registers are provided and are within the acceptance criteria (Refer Annex 1 EU GMPs). Critical sterile stages for DS manufacturing are the inoculation of WCB and filling of DS. ○ Non-viable particle monitoring available and within the acceptance criteria ○ Microbiology monitoring available and within the acceptance criteria	✓	
➤ Manufacturing yield of all relevant manufacturing steps registered and within the acceptance criteria	✓	
➤ Deviations and CAPA registered, and deviation reports provided. They are reviewed and accepted. See comments	✓	
➤ Change Controls registered and provided. They are reviewed and accepted. ○ Are Change Controls registered with regulatory impact? Yes ☐ No ☒ If so, variation approval and updated relevant sections of the CTD should be provided, reviewed and in accordance with the change. Statement with the list of changes related to the current product is shared. Regulatory impact and actions are assessed by Celltrion and documented. See comments.	✓	
➤ Batch Manufacturing Record of Drug Substance in compliance with CTD and Marketing Authorisation.	✓	

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	✓	N/A
➤ BMR QA supervision and signature	✓	
➤ Master batch record approved, and its change control associated.	✓	
Certificate of analysis (CoA) of Drug Substance		
➤ Certificate of analysis reference number Certificate number: DS22200P006002	✓	
➤ Analytical parameters, specifications and analytical methods according to CTD and Marketing authorisation. Internal specifications: MSP4406 (1.0.0)	✓	
➤ Deviations and OOS reference registered, if any See comments	✓	
➤ Results: Complies	✓	
Batch manufacturing record of bulk and /or finished product ☒ N/A		
➤ Bulk batch identification.		
➤ Batch manufacturing record edition and approval for bulk and finished product (if different).		
➤ All attachments (if any) to the Batch Manufacturing Record are received and reviewed. Ensure that critical records for sterile products are available, reviewed, and show results within the approved specifications/parameters. Select the documentation reviewed: ○ Aseptic filling: Filter integrity tests pre and post product filtration ☐		
➤ Batch size in accordance with the CTD (3.2.P).		
➤ In the Batch Record and supporting documentation, the raw data is recorded according to Good Documentation Practices		
➤ The Batch Record includes the registry and approval of starting materials (API, excipients), and they are within the validity period.		
➤ The Batch Record includes the registry of equipment, calibration/qualification status and cleaning status (attached status labels if necessary). All are within validity period.		
➤ The Batch Record properly documents line clearance.		

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	✓	N/A
➤ All registered in-process controls are appropriately carried out and comply with the acceptance criteria defined in the CTD (3.2.P).		
➤ Environmental controls registers are provided and are within the acceptance criteria. For sterile products (Refer Annex 1 EU GMPs). ○ Non-viable particle monitoring available and within the acceptance criteria ○ Microbiology monitoring available and within the acceptance criteria		
➤ Manufacturing yield of all relevant manufacturing steps registered and within the acceptance criteria		
➤ Deviations and CAPA registered, and deviation reports provided. They are reviewed and accepted.		
➤ Change Controls registered and provided. They are reviewed and accepted. ○ Are Change Controls registered with regulatory impact? Yes ☐ No ☐ If so, variation approval and updated relevant sections of the CTD should be provided, reviewed and in accordance with the change.		
➤ Certificate of Compliance for DS available		
➤ Batch Manufacturing Record of bulk in compliance with CTD and Marketing Authorisation.		
➤ BMR QA supervision and signature.		
➤ Master batch record approved, and its change control associated.		
Batch packaging records of marketed finished product	☒	N/A
➤ Batch packaging identification.		
➤ Batch packaging record edition and approval for primary and secondary (if different).		
➤ Packaging operations are dully registered.		
➤ In the Batch Record and supporting documentation, the raw data is recorded according to Good Documentation Practices.		
➤ The Batch Record includes the registry and approval of packaging materials, and they are within the validity period.		
➤ The Batch Record includes the registry of equipment, calibration/qualification status and cleaning status (attached status labels if necessary). All are within validity period.		

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	✓	N/A
➤ The Batch Record properly documents line clearance.		
➤ All registered in-process controls are appropriately carried out and comply with the acceptance criteria defined in the CTD (3.2.P).		
➤ Environmental controls register available and within the acceptance limit		
➤ Primary and secondary packaging material and leaflet are approved with a copy endorsed in the batch record.		
➤ Reconciliation of packaging materials and units of finished products. Results meet the defined acceptance criteria, if any.		
➤ Deviations and CAPA registered, and deviation reports provided. They are reviewed and accepted.		
➤ Change Controls registered and provided. They are reviewed and accepted. ○ Change Controls with regulatory impact: Yes ☐ No ☐ If so, variation approval and updated relevant sections of the CTD should be provided, reviewed and in accordance with the change.		
➤ Batch packaging record of finished product in compliance with CTD and Marketing Authorisation.		
➤ BPR QA supervision and signature.		
➤ Master batch record approved, and its change control associated.		
Artworks and Antifalsified revision		☒ N/A
➤ Revision of the name of the product, strength, batch number, dosage form and expiry date in primary, secondary and tertiary packaging. All aspects are in compliance with CTD and Marketing Authorization.		
➤ Revision of the antifalsified measures and devices: serialized units (unique SN and Data Matrix) and tamper evident. Verify that they are in compliance with regulation.		

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	✓	N/A
➤ Revision of the Artworks versions according to authorised artworks from CTD and Marketing Authorisation. Revision that the artworks are approved (signed) by MAH. ○ Artwork Code and version Primary packaging: ○ Artwork Code and version Secondary Packaging: ○ Artwork Code and version Leaflet:		
Certificate of Conformity (CoC) issued by the manufacturer		
➤ Name of the product CT-P41 Drug Substance	✓	
➤ Strength and dosage form		✓
➤ Batch number 22200P006	✓	
➤ Quantity released (units) 454.582 kg in 5 bottles of 1L, 5 bottles of 2L and 46 bottles of 10L	✓	
➤ Manufacturing date 01.11.2022	✓	
➤ Expiry date (<i>Register the approved shelf life</i>) 31.10.2026 (48 months at -75°C±15°C)	✓	
➤ Deviation, if any, registered and available (Deviations, change control, OOS and/or CAPA reference) See comments	✓	
➤ Certification statement	✓	
➤ CoC signed by Qualified Person or QA Manager (<i>name, date and signature</i>) Signed by QA 16.07.2025	✓	
Certificate of analysis (CoA) of Drug Product issued by the manufacturer		☒ N/A
➤ Certificate of analysis reference number		
➤ Analytical parameters, specifications and analytical methods according to CTD and Marketing authorisation.		
➤ Deviations and OOS reference registered, if any		
➤ Results: Complies		
Certificate of analysis (CoA) of Drug Product issued by Kymos		☒ N/A
➤ Certificate of analysis reference number		

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	✓	N/A
➤ Deviations and OOS reference, if any.		
➤ Results: Complies		
Transport and storage conditions	☒ N/A	
➤ Transport route and Data logger ID. Verify that the temperatures during shipping are within the registered storage conditions of the product.		
➤ Deviations, if any If deviations are registered during transport, deviation reports are provided, reviewed and accepted.		
➤ Temperature evaluation report during the shipping of the batch or equivalent document provided and approved by the company responsible of the transport/MAH. ☐ If yes , it is reviewed and accepted. ☐ If not , temperature during the shipping of the batch to be evaluated (<i>Register data logger reference, T_{min} and T_{max} and the impact on the quality of the product</i>).		
➤ Storage temperature records for products requiring special storage conditions (e.g., 2-8°C, -20°C) should be available, reviewed, and within the acceptance criteria.		
Packing list		
➤ Packing list available for each transport route and contains dataloggers information, quantity of units shipped, weights and dimensions (<i>List transport routes and packing list references</i>)		✓
➤ The quantity of units shipped corresponds to the units released by the Finished Product Manufacturer		✓
Incoming inspection of goods into warehouse (after importation)	☒ N/A	
➤ Review of the document identification, date of arrival of goods at the warehouse, and confirmation of conformity.		
QC samples, reference and retention samples	☒ N/A	

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	✓	N/A
➤ Verification of sampling records ○ Sampling carried out at EU warehouse ☐ ○ Sampling carried out at third-country manufacturing site ☐ Verify that all relevant sampling documents and records are available and reviewed		
➤ Verification of the QC samples: an adequate number of units are available to conduct full batch testing Number of units:		
➤ Verification of reference and retention samples: an adequate number of units are available to conduct 2 times a full batch testing Number of units:		
➤ Location of the stored reference and retention samples is checked Location:		
Commissioning and decommissioning of the batch, QC, reference and retention samples ☒ N/A		
➤ Commissioning and decommissioning records are provided, reviewed, and correspond with released units, QC, and reference and retention samples.		
➤ If N/A justify:		
Pictures of the Finished Product (including artworks and variable data)		✓
Batch Release Certificate (LIMS Batch Release Certificate)		
➤ Product Trade Name (same name as packaging) Denosumab (CT-P41) Drug Substance	✓	
➤ Marketing Authorisation Number EU/1/24/1904 (Vial) EU/1/24/1905 (PFS)	✓	
➤ Strength/Potency DP: CT-P41 120 mg (Vial) ; CT-P41 60 mg (PFS)	✓	
➤ Dosage form Bottles	✓	
➤ Type and size of packaging 1 Litre, 2 Litres and 10 Litres bottles	✓	
➤ Batch Number 22200P006	✓	
➤ Quantity Released (consider the units to be withdrawn, if applicable) 454.582 kg in 5 bottles of 1L, 5 bottles of 2L and 46 bottles of 10L	✓	
➤ Manufacture date (dd/mm/yyyy) 01/11/2022	✓	

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	✓	N/A
➤ Expiry date (dd/mm/yyyy) 31/10/2026	✓	
➤ Destination country/ies EU/EEA	✓	
➤ Comments/Remarks (deviations, customer's requirements, etc.) Deviations: DE2-2022-191, DE2-2022-203 and DE2-2022-209	✓	
➤ Certification statement duly completed	✓	
➤ Batch Release Certificate sent to QP in LIMS System.	✓	

COMMENTS:

- **Review of documents provided (Batch records, Certificate of analysis and CoC):**

See comments archived in related batch release folder.

Some discrepancies were identified between the IPC acceptance criteria defined in the BMR and those specified in the CTD. It has been verified that all results obtained for the current batch met the acceptance criteria approved in the CTD. A justification has been requested from Celltrion regarding these differences, which are due to the fact that the current batch is a Process Validation (PV) batch. The specifications were updated in Celltrion in accordance with Change Control PR66973 (Upstream process) and PR67997 (Downstream process) for commercial batches, aligning with the approved CTD. A re-evaluation of the manufacturing process has been conducted by Celltrion, as documented in QA4061-A3, covering both the Upstream and Ultrafiltration/Diafiltration processes. This assessment confirms that all IPC results complied with the approved specifications. Additionally, the IPT Memorandum issued by Celltrion QA confirms that the approved registered specifications have been met. See related documentation in batch folder "Re-evaluation manufacturing process PV-commercial".

- **Regarding deviations to the manufacturing and packaging process of DS:**

Statement of Deviations and Change Controls on this batch of Drug Substance provided by Celltrion.

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Deviations registered are detailed below:

Deviation code	Classification	Description	Status
DE2-2022-191 (PR 50690)	Major	(nCPP Excursion) Excursion of Load Conductivity on Capto Adhere chromatography step for 2200P001 batch. The root cause of the investigation was identified as the WFI dilution factor which is not suitable for production at a large scale specified in the manufacturing record. The conductivity was met when 1.3 dilution ratio was applied in 2200P002-2220P007 batches. However, 200P Process Description and MBR should be revised through a CAPA to perform additional dilution according to the measured conductivity after applying the initial dilution ratio at 1.0.	Closed
DE2-2022-203 (PR 51481)	Major	Failure of Bioburden test for P2-V-1542, P2-DFS-1520 and T-line to P2-V-1542 rinse sample during cleaning verification. Due to incorrect gasket installation in the sampling port, water (environmental) in which microorganisms may remain in the sampling port, there is a possibility that bacteria entered in the water remaining in the sampling port in the Tech core, so there is the possibility that may not have been completely removed through disinfection and flush procedures between sampling operations.	Closed
DE2-2022-209 (PR 51941)	Critical	Expanded investigation for OOS results of HCP (QC4347) for Mab & VI Pool samples, result obtained 1.196 ppm. During 2LIR-2022-106 OOS result was confirmed and no root cause was identified except for Pool residual HCP specification narrowly set based on the limited data. Current and approved specification for this parameter is ≤ 10 ppm.	Closed

After risk evaluation for deviation, it was concluded not to compromise the quality of the product.

Laboratory Investigation Report registered is detailed below:

- Laboratory Investigation 2LIR-2022-106 is registered and related to deviation **DE2-2022-209**.
- Out of In-Process Trend Investigation **OIPT-2S-22-050** is also registered and investigation is carried out related to the identification of bacteria in neutralized Mab Prisma Eluate at last cycle (Pre-filtration) from batches 22200P004 to 22200P007. Nevertheless, all bioburden results met the specifications ≤ 100 CFU/10ml. The cause was confirmed to be a packing plate leak at the top of the column according to the investigation **OIPT-22-22-049**. It is concluded that although microorganisms were found in some swabs samples, it is likely that the issue was with the column itself and it is unlikely that there were bacteria in the process stream itself, so it was confirmed that there was no impact on the quality of the product. As it is not considered a deviation in Celltrion's Quality System, it is not included in the CoC issued by Kymos.

Change Controls:

See summary of related **change controls** also included in the Statement of Deviations and Change Controls on Drug Substance.

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Performed by:

Reviewed by: