STANDARD OPERATING PROCEDURE

Drug Product Qualification and Monitoring of CSP for Batch Documentation Review	**Document #:**	SOP-RQA-0155
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1.0 PURPOSE

The purpose of this SOP is to describe the process for qualification and monitoring of Contract Service Providers (CSP) for batch record review and/or lot disposition.

2.0 SCOPE

This SOP applies to Drug Product and Finished Drug Product manufactured under cGMP regulations for [COMPANY NAME REDACTED] for use in toxicology studies, clinical trials, and commercial distribution.

3.0 RESPONSIBILITIES

3.1 Quality Assurance (QA) is responsible to:

3.1.1 Qualify, monitor and re-evaluate CSP for batch record review and/or disposition.

3.1.2 Complete batch record review and/or disposition as required following SOP-RQA-0041.

3.1.3 Notify the CSP and other stakeholders of the disposition status of the batch/lot.

3.1.4 Archive the completed executed batch record, forms and reports following SOP-RQA-0041.

4.0 REFERENCES

- FRM-RCQ-0109, Controlled Document Change Request (CDCR)
- FRM-RQA-0133, Drug Product QA Disposition Certificate
- FRM-RQA-0134, Drug Product QA Disposition Checklist
- FRM-RQA-0136, Drug Product Batch Disposition Notification for CSP
- FRM-RQA-0176, Drug Product Qualification Form

- FRM-RQA-0177, Drug Product CSP Notification of Qualification Status
- SOP-RQA-0041, Drug Product Batch Record Review and Disposition
- 21CFR Part 211.192, current Good Manufacturing Practice regulations, Production Record Review
- ICH Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

5.0 DEFINITIONS AND ABBREVIATIONS

- **cGMP/GMP**: current Good Manufacturing Practice
- **GDP**: Good Documentation Practices
- **COA**: Certificate of Analysis
- **COC**: Certificate of Conformance
- **MBR**: Master Batch Record
- **NCMR**: Non-Conforming Material Report
- **OOS**: Out of Specification
- **OOT**: Out of Trend
- **SOP**: Standard Operating Procedure
- **Batch/lot**: a specific quantity of material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing run during the same cycle of manufacture.
- **Contract Manufacturing Organization (CMO)**: an outside manufacturing organization engaged by [COMPANY NAME REDACTED] for performing synthesis, formulation, filling, testing, packaging, labeling, warehousing and/or distribution of drug substance or drug products in compliance with cGMPs.

- **Contract Service Provider (CSP)**: any organization separate from [COMPANY NAME REDACTED] that provides GMP assay/process development, manufacturing, testing, labeling, packaging, warehousing, distribution, calibration, maintenance, or any other GMP related services. Examples of CSPs are Contract Manufacturing Organization (CMOs), and Contract Testing Laboratories (CTL).

- **Drug Product**: The polymerization step for manufacturing of API for Veltassa. The finished dosage form that contains API and excipient.

- **Executed Batch Record (EBR/batch record):** a collection of documents pertaining to the release of a batch/lot. The types of documents included in the EBR include, but are not limited to, copies of:

    - executed batch records from the CSP,
    - any discrepancy reports (e.g., deviation reports, OOS results, investigations, etc.),
    - vendor COAs,
    - ancillary documentation provided by the CSP.

- **Finished Drug Product:** A finished dosage form that contains API and excipients, and that is lab\eled and packaged for shipment to [COMPANY NAME REDACTED] or its designee.

- **GDP Error**: Notation errors in documentation which have no serious implications or are easily comprehended. More severe GDP errors should be treated as Deviations. GDP Error examples include: no initial and date crossout, illegible text, etc.

6.0 PROCEDURE

Refer to Attachment 1, Process Diagram for Qualification of CSP for Drug Product Review, for the overview of the qualification process.

6.1 Qualification

6.1.1 The CSP performs a 100% review of EBR for each lot. [COMPANY NAME REDACTED] performs 100% review of EBR for each lot according to SOP-RQA-0041. CSP evaluated as follows:

a. 100% deviations identified, documented and reports closed.

b. 100% change control reports identified and documented.

c. 100% critical steps documented correctly and met required limits.

d. <10 good documentation errors found in BR.

e. No trends noted during the qualification review of that would necessitate corrective action.

6.1.2 For each EBR reviewed, [COMPANY NAME REDACTED] QA completes FRM-RQA-0176, to be filed with the assembled EBR, as appropriate.

6.1.3 Depending on the outcome from FRM-RQA-0176, [COMPANY NAME REDACTED] QA qualifies the CSP using FRM-RQA-0177, and uses the same form to communicate results to the CSP.

a. If the CSP met these criteria for a statistically determined number of consecutive lots, the CSP is approved as Qualified to perform EBR review. CSP will now be subject to Monitoring by [COMPANY NAME REDACTED] QA (see 6.2.).

b. If the CSP does not meet these criteria for a statistically determined number of consecutive lots, the review continues until sufficient consecutive lots meet the standards. If appropriate, [COMPANY NAME REDACTED] QA may issue a CAPA instructing CSP of mitigations of observed problems in their Quality Assurance processes.

6.2 Monitoring

6.2.1 CSP performs a 100% review of EBR for each lot. [COMPANY NAME REDACTED] does a reduced review for each lot (according to SOP-RQA-0041) by reviewing:

a. Deviations & OOSs,

b. Batch record comments and process notes

c. CSP batch certificates

d. CSP COA

6.2.2 If [COMPANY NAME REDACTED] QA determines that the reviewed materials contained errors that were improperly addressed by CSP QA, the CSP loses its Qualified status. It may reapply for Qualification as per the CSP does not meet these criteria on a statistically determined number of consecutive lots, the review continues until get three consecutive lots meet the standards.

6.2.3 If the CSP is disqualified, [COMPANY NAME REDACTED] QA issues:

a. FRM-RQA-0177, with any relevant documents attached.

b. A CAPA notifying CSP of the necessary mitigations before they can apply again for Qualification.

c. A CAPA for [COMPANY NAME REDACTED] QA to do a 100% EBR review of all lots reviewed by the now Disqualified CSP, since the last time [COMPANY NAME REDACTED] QA qualified them. If they have never been qualified, all lots must be reviewed.

6.3 Requalification

6.3.1 If the CSP has lost its Qualification status and has performed the Corrective and Preventive Actions prescribed by [COMPANY NAME REDACTED] QA, [COMPANY NAME REDACTED] QA may perform a 100% EBR review on a statistically determined number of lots. This number may be increased by

[COMPANY NAME REDACTED] QA using risk management. Use the procedure in 6.1 to guide the requalification of the CSP.

7.0 RECORDS

7.1 QA archives the completed executed batch record, forms, and reports following SOP-RQA-0041.

7.2 FRM-RQA-0176 and FRM-RQA0177 will be filed with the relevant EBR(s) reviewed, and electronically (i.e. EDMS)

8.0 ATTACHMENTS

- Process Diagram for Qualification of CSP for Drug Product Review.

8.1

[redacted]

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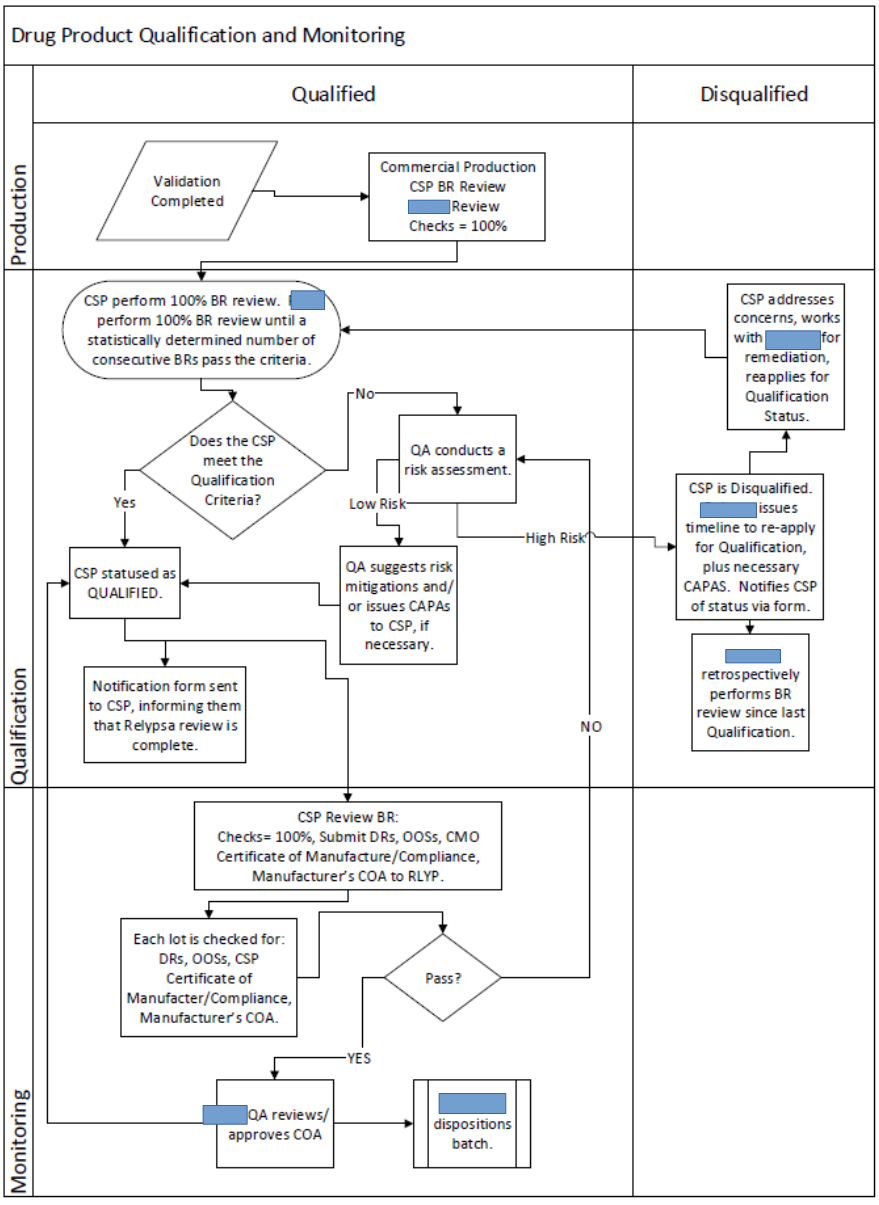
Attachment 1: Process Diagram for Qualification of CSP for Drug Product Review



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REVISION HISTORY

Revision #	Summary of Changes
00	New SOP. See Revision history for SOP-RQA-0130 (Revision 00) for revision details.