REQUESTING A QUALITY ASSURANCE STUDY REVIEW FROM THE QUALITY ASSURANCE TEAM

I. PURPOSE

This document describes the procedure to request a Quality Assurance Study Review from a quality assurance study reviewer (QASR) on the Quality Assurance (QA) Team (HFV-184) for submissions with safety, effectiveness, and bioequivalence data. These submissions are typically Submission Tracking and Reporting System (STARS) P submissions to an investigational new animal drug (INAD) or generic investigational new animal drug (JINAD) file or in a traditional abbreviated or new animal drug application ((A)NADA). Based on current processes, the P submissions received by the Division of Animal Bioengineering and Cellular Therapies will not be undergoing a Quality Assurance Study Review. This document also describes what the QASR will do when conducting their review and provides timeframes associated with the steps in the process.

II. QUALITY ASSURANCE STUDY REVIEW PROCESS

A QASR on the QA Team will perform a Quality Assurance Study Review on a submission that contains effectiveness, safety (target animal safety or human food safety), or bioequivalence studies with data. The QASR consulting review will commence after the Refuse to Review/Refuse to File assessment has been completed by the primary review division and the QASR has been notified that the submission is acceptable for further review. A Refuse to File assessment will be conducted by the primary review division for applications and a Refuse to Review will be conducted for submissions under a INAD or JINAD file (See P&P 1243.3100 and P&P 1243.2050).

The Appendix contains a flow chart summarizing the process for the Quality Assurance Study Review of a data submission including timeframes for each step.

Prior to initiating the review, the QASR will notify the primary reviewer (PR) that the Quality Assurance Study Review is starting. The PR can discuss any issues or concerns with the QASR. Regular communication will continue throughout the review process.

The Quality Assurance Study Review is conducted in two parts: the submission screen and the full study review.

A. Submission Screen

Screening the submission or the submission screen is the first phase of the Quality Assurance Study Review. This is a screen conducted to confirm that all necessary documents and data are included for each study in the submission or application that will be used to support scientific and regulatory decisions. The QASR will select the appropriate submission screen template depending on the type(s) of studies included in the submission or application and their stated standards of conduct [i.e., Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)]. Although there is occasional variation, typically submissions with STARS subclass codes of EF have studies conducted in accordance with the GCP guidance (GFI #85). Submissions with STARS subclass codes of TS, HF, and BE typically have studies conducted in accordance with the GLP regulations (21 CFR part 58). If the submission contains a mixture of studies, such as a traditional application, the QASR will modify the screen as appropriate to accommodate the submitted studies.

While conducting the submission screen, the QASR will:

1. Review the final study report and protocol for each study in the submission to determine they are present, reasonably complete, and all relevant categories of raw data copies and contributor reports were included in the submission (per the study protocol and ONADE policy regarding requirements for raw data).

2. Identify the method(s) of data collection and appropriate corresponding information or data files in the submission.

The target completion date of the submission screen is Day 50 of the review clock. If significant deficiencies are identified, the QASR will provide "Transmit to Sponsor" comments and will ask the PR to request an amendment. The data submissions with a shortened review time will not undergo a submission screen and only a full study review will be performed.

It is possible that the number and nature of the significant deficiencies found may prompt the QASR reviewer to request the submission be refused to review. If this situation arises, the determination for how to move forward will be discussed and agreed upon by the review team.[1] Alternatively, if a technical section incomplete is determined to be the appropriate final action for the submission by the review team, the QASR will provide "Transmit to Sponsor" comments to the PR for the technical section incomplete letter.

B. Full Study Review

The full study review is the second phase of the Quality Assurance Study Review and is started after the submission screen has been completed. For submissions with shortened review time, the QASR review process will be modified to meet the required consulting timelines. At this step, the QASR will proceed with the full

[1] For the purposes of this process, the Review Team is the primary reviewer and all consulting reviewers involved in the review of the submission, including the QASR.

study review if the submission has been determined to be acceptable for further review. The QASR will also review any amendments made to the submission.

While conducting the full study review, the QASR will:

1. Confirm the final study report accurately describes the conduct of the study and that the study was conducted in accordance with the protocol and any amendments or deviations documented.
2. Confirm the final study report accurately reflects the copies of raw data (study documentation) submitted.
3. Confirm the standard of conduct (typically GLP or GCP) stated in the protocol appears to have been followed.
4. Provide an assessment of study and data quality and identify any issues of the study or data quality that should be further evaluated via a Bioresearch Monitoring (BIMO) inspection or addressed by the submission of additional information by the sponsor.

The QASR will perform a complete data quality review, but the QASR's Transmit to Sponsor comments will focus on the following five critical areas:

1. Drug Accountability
2. Dosage to Animal
3. Animal Accountability and Enrollment
4. Study Endpoints and Critical Variables
5. Adverse Events

Issues outside of these five areas of focus will be discussed in the Quality Assurance Study Review but will not result in Transmit to Sponsor comments unless the issues are egregious and impact the quality and integrity of the study or data. In addition, any protocol deviation identified by a QASR but not discussed in any manner in the submission will result in a Transmit to Sponsor comment, asking the sponsor to provide documentation for the deviation that includes:

- The date the deviation occurred;
- a description/explanation of the deviation;
- any corrective or mitigating action that was undertaken to address the deviation, if appropriate; and
- the impact of the deviation on the study.

The documentation of the deviation should meet the basic standards expected for all raw data: attributable, legible, contemporaneous, original, and accurate (ALCOA). Often the QASR will recommend that quality issues be evaluated by appropriate members of the review team to determine their impact on the

acceptability of the study and the necessity of any further action by CVM or the sponsor.

III. QUALITY ASSURANCE STUDY REVIEW REQUEST: GENERAL INFORMATION

A. QASR Responsibilities

While conducting a Quality Assurance Study Review, the QASR will:

1. Review the submission for study and data integrity issues using team Standard Operating Procedures (SOPs), templates, and checklists specific to the type of study being reviewed,
2. Assess the quality and credibility of the data and final study report, and
3. Communicate with other members of the review team if issues are identified.

It is important to note that the QASR will utilize his or her quality assurance expertise to assess the quality of the submission. Critical gaps in data quality will result in Transmit to Sponsor comments. Other data quality issues will be identified for the PR to assess when determining if issues found impact the study(ies) acceptability to support the approval of the new animal drug.

B. Contacting the Quality Assurance Team Leader

The PR should contact the QA Team Leader (QA TL) via email and request a consult for a Quality Assurance Study Review. This request should be made before a formal consult is requested in Appian. The subject line for the email request should state that the email is requesting a QASR consulting review and the submission identifier as follows “Request for QASR Consult; X-XXXX-X-XXXX (XX).” Any pertinent background information or special considerations should be included in the email request.

The QA TL will review the STARS pending lists of the team and determine if the resources are available to accept a consult. Within three business days the QA TL will respond to the requester’s email. In special cases where study and data quality are of specific concern, the PR should contact the QA TL to discuss the package and timing of the Quality Assurance Study Review.

C. Creating the QASR Request Consult in Appian

Once the PR has received confirmation that the QA Team can accept a consult, the PR will request a formal QASR consult in Appian according to the procedures in P&P1243.3200. Any critical information about the submission should be provided by the PR in the instructions section of the consult.

D. Assignment of QASR Consults

Once the QA TL receives the Appian notification for the request for a QASR consult, he or she will assign the consult to a QASR.

E. Review of the QASR's Draft Review

When the QASR sends the draft review to the QA TL, the QASR will also send a copy of the draft review to the PR and any other members of the review team designated by the PR. The review will be identified as draft in that it will have a watermark that says DRAFT. The QASR will schedule a meeting with the PR and additional attendees determined by the PR. to discuss the findings of the QASR and address questions or concerns. If the QASR determines that a BIMO inspection is needed, the QASR and PR will coordinate the completion of the necessary request forms (see P&P 1243.8215). Every effort will be made by the QASR to schedule this meeting before the finalization of the QASR review. At the meeting, the review team will discuss the QASR findings and discuss any potential revisions to the QASR review.

F. Returning QASR Consults

Once the Quality Assurance Study Review is completed and ready to finalize, the QASR will upload the review and return the consult to the PR in Appian-Tempo (see P&P 1243.3029). The final QASR review will be returned by Day 130 as per the consulting due date established in STARS for data submissions.

IV. REFERENCES

CVM Program Policies and Procedure Manual – ONADE Reviewer's Chapter

1243.2050-Refuse to File and Refuse to Review

1243.3029- Closing Out Consulting Reviews for Submission Tracking and Reporting System (STARS) submissions

1243.3100- Refuse to Review (RTR) and Refuse to File (RTF) Assessment of Submissions and Applications That Contain Data

1243.3200- Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

V. VERSION HISTORY

October 11, 2018 – Original version.

May 6, 2021 – Updated titles in the reference section and reflect that there is now a Division of Animal Bioengineering and Cellular Therapies.

APPENDIX - QUALITY ASSURANCE STUDY REVIEWER (QASR) REVIEW PROCESS WORKFLOW