INTEGRATING AN END-REVIEW AMENDMENT (ERA) INTO THE INVESTIGATIONAL NEW ANIMAL DRUG PROTOCOL (E) SUBMISSION REVIEW PROCESS

I. PURPOSE

This document describes the procedures for:

- Integrating an end-review amendment (ERA) into the investigational new animal drug (INAD) protocol (E) submission review process.

II. BACKGROUND

The Animal Drug User Fee Amendments of 2008 (ADUFA II) provides for the use of the ERA process to enhance the review of INAD protocol (E) submissions.

The ADUFA II Goals Letter states, "The term 'end-review amendment (ERA)' is understood to mean an amendment to an … investigational animal drug submission

that is requested by CVM after it has completed its review of the submitted information and determines that the submission of additional non-substantial data or information would likely complete the … submission. This term does not include minor amendments that are requested by CVM during review of … submissions ….”

There are different performance goals (i.e., ADUFA deadlines) for the review of protocols, based on whether we request an ERA and whether we receive a requested ERA on time.

If we consider a protocol acceptable (i.e., we concur with the protocol), the ADUFA deadline for completing the review of the protocol and notifying the sponsor electronically (i.e., via email) is 50 days, with a concurrence letter issued by Day 60. [1] [2]

If we do not consider a protocol acceptable based on the submitted information and we do not request an ERA, the ADUFA deadline for completing the review of the protocol and notifying the sponsor electronically (i.e., via email) is 50 days, with a non-concurrence letter issued by Day 60.

If we determine that an ERA would likely allow us to complete a review of the protocol and reach a decision on whether it is acceptable, the ADUFA deadline for requesting the ERA electronically (i.e., via email) is 50 days.

If we request an ERA and we do not receive it within 10 days of the request, then the ADUFA deadline for completing the review of the protocol (without the ERA) and issuing a non-concurrence letter is 75 days.

If we request an ERA and we receive it within 10 days, then the ADUFA deadline for completing the review of the protocol, incorporating the ERA, is 20 days after receiving the amended protocol (but no less than 60 days or more than 80 days after receiving the original protocol).

The ADUFA II Goals Letter language pertaining to the performance goals for protocols is in Appendix 1.

[1] From the ADUFA II Goals Letter -- “Completing the review” means conducting a complete and comprehensive review of the available information, then issuing an action letter which either (1) notifies a sponsor that an investigational animal drug submission is complete or (2) sets forth in detail the specific deficiencies in the submission and, where appropriate, the actions necessary to place the submission in condition for approval.

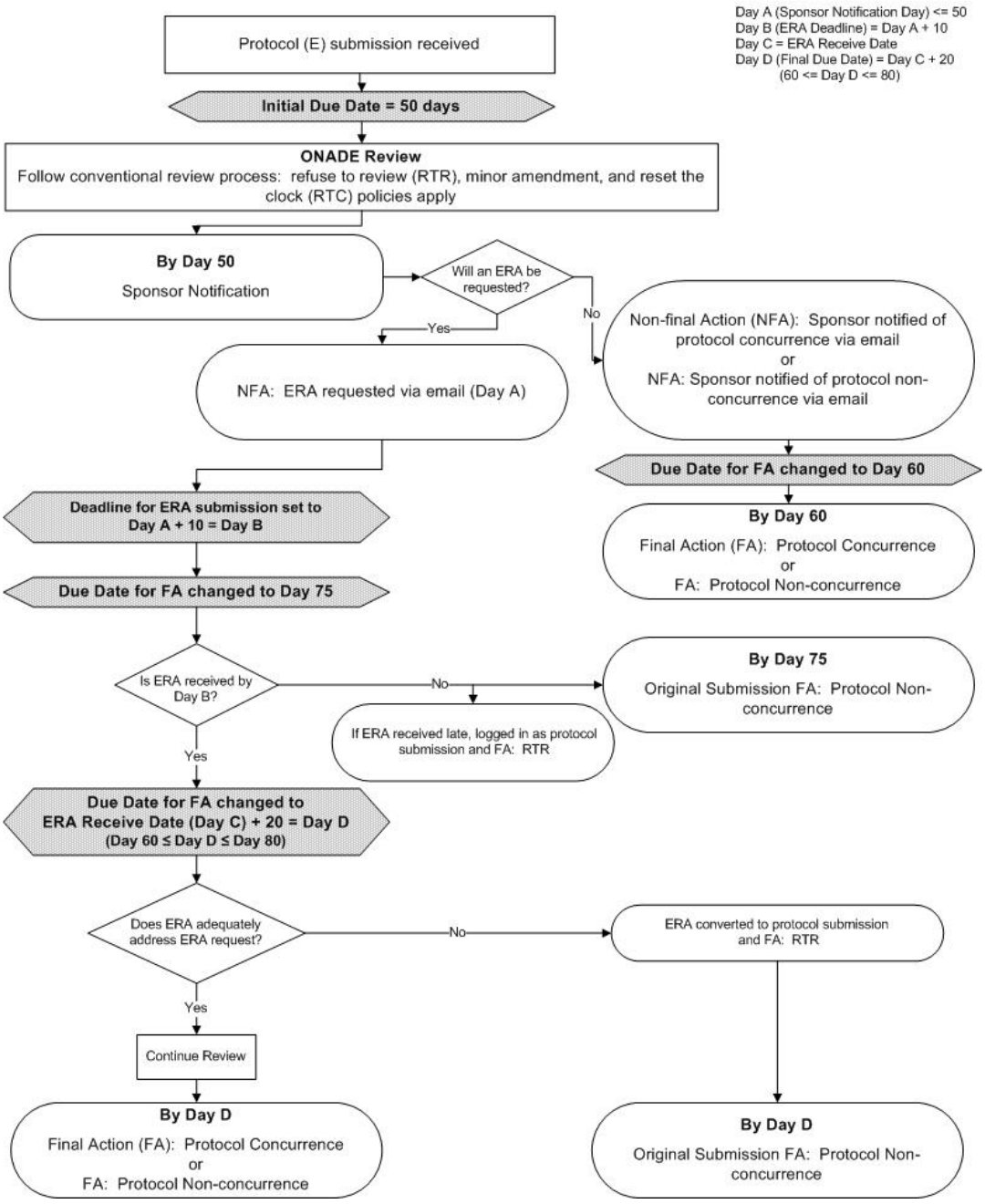
[2] Unless otherwise stated, all timeframes reference the date that a submission is received by CVM’s Document Control Unit (DCU).

III. ERA PROCESS FLOWCHART

The following flowchart shows the review process for protocols, including key ADUFA deadlines, as it relates to the ERA.

End Review Amendment Process:

Protocols Without Data (E) Submissions



IV. KEY DATES

The following are key dates in the review of protocols. The following have to occur on or before the indicated day:

Day 50 – Refuse to review (RTR), if applicable[3]

Day A (on or before Day 50) – Non-final Action (NFA) – Sponsor notification via email. Three options:

1. Sponsor notified of our intent to issue a protocol concurrence letter; email sent (NFA Code 078: NOTIFY YES)

2. Sponsor notified of our intent to issue a protocol non-concurrence letter; email sent (NFA Code 079: NOTIFY NO)

3. ERA requested from sponsor; email sent (NFA Code 077: ERA REQSTD)

Day 60 – If no ERA requested on or before Day A (Day 50), two options:

1. Final action (FA) – Protocol Acceptable as Submitted; Letter Sent (FA Code 045: PROT CONCR)

2. FA – Protocol Not Acceptable as Submitted; Letter Sent (FA Code 046: PROT NCONC)

Day B (Day A + 10) – If ERA requested, ERA must be received within 10 days of ERA request

Day C – Day that we receive the ERA

Day 75 – If requested ERA not received by Day B: FA – Protocol Not Acceptable as Submitted; Letter Sent (FA Code 046: PROT NCONC)

Day D (Day C + 20: cannot be less than Day 60 or greater than Day 80) – If requested ERA received within 10 days of ERA request (on or before Day C), two options:

[3] Guidance for Industry #119 and ADUFA II Goals Letter: Within 60 days of submission, FDA will refuse to review (RTR) an INAD submission which is determined to be insufficient on its face or otherwise of unacceptable quality upon initial inspection using criteria and procedures similar to those found in 21 CFR 514.110. Because of the ADUFA deadline of 50 days for CVM to notify the sponsor of protocol action, RTR must be done on or before Day 50.

1. FA – Protocol Acceptable as Submitted; Letter Sent (FA Code 045: PROT CONCR)

2. FA – Protocol Not Acceptable as Submitted; Letter Sent (FA Code 046: PROT NCONC)

V. REVIEW OF PROTOCOLS UP TO DAY 50

The review of protocols should follow conventional division review procedures, including refuse to review (RTR), reset the clock (RTC), and minor amendment procedures, before the first ADUFA deadline of Day 50.[4] [5] [6]

A. Protocol Submission Timeline

The primary reviewer (PR) and any consulting reviewers follow the timeline developed for protocol review (submission timeline). This timeline includes interim key dates, such as the date by which the review team meets to discuss the protocol, the dates by which consulting reviews are completed, and ERA-related key dates.

B. Communication

Communication is essential among the review team members (PR and consulting reviewers). If any reviewer wants a minor amendment, the reviewer should contact the PR, who coordinates with the review team to minimize individual amendment requests to the sponsor. All the review team members are responsible for informing each other immediately if they run into an issue that may make the protocol unacceptable.

C. Reviews

All primary and consulting reviews throughout the review process need to be complete (i.e., signed and on yellow paper) according to the submission timeline, whether or not an ERA is requested. The primary reason reviews need to be complete prior to the request for the ERA is because the ERA is a formal process that is linked to the ADUFA II performance goals. Thus, ERA request emails

[4] See P&P 1243.2050.
[5] See P&P 1243.3026.
[6] See P&P 1243.4060.

issued by CVM during this process have the same significance as letters signed by the division directors and team leaders. Therefore, all reviewers must complete their reviews according to the submission timeline.

In addition to the formal nature of the ERA process, there are logistical issues that mandate completed reviews. For example, with protocols, if we do not receive a requested ERA within 10 days, we must issue the protocol non-concurrence letter for the submission by Day 75. This very short timeline necessitates that the PR have all completed reviews in order to process the letter administratively.

1. Electronic Protocol Submissions

   The Outlook Notification Form Integration (ONFI) system that ONADE used to route electronically-submitted protocols and their associated review documents through the review process is no longer available for electronic protocols. However, sponsors can continue to submit protocols electronically through the CVM electronic submission gateway and reviewers will continue to have access to the electronic protocols via STARS to facilitate their reviews.

   Primary and consulting review divisions will move and process the electronically-submitted protocols using current procedures for paper submissions.

   Note the following important two changes:

   - Because ONFI is not available, the PR will not receive an email notification that they have a new electronic submission, nor will they receive a hard copy. The primary review divisions will notify the PR of the pending protocol per division procedures.

   - To send a consult, the PR prints a blank Review Request and Movement Form, attaches the completed form to an empty manila folder and places it in the DCU pick-up box. The PR should write in the "For Reviewers Use" box that the protocol is electronic.

2. Consulting reviews

   Consulting reviews are due by the date indicated in the submission timeline.

The completed review includes the consulting reviewer's recommendation: (1) concur with the protocol, (2) do not concur with the protocol, or (3) request an ERA. If the consulting reviewer recommends an ERA, then the consulting review provides specific comments for the ERA request in the Transmit to Sponsor section of the review. (For definition and scope of an ERA request, please see Appendix 2.)

The consulting review file name contains the submission number and the alphanumeric designation of the consulting review, followed by ".rev". (Please see Appendix 3 for file-naming conventions.) For example, the biometrics A1 consulting review for submission E0019 is named "E0019a1b.rev".

Return the consulting review to the PR using current procedures.[7]

3. The PR, in consultation with their team leader and the consulting reviewers as needed, evaluates the recommendations from PR review and all consulting reviews to determine the appropriate final action or non-final action (i.e., ERA request). The PR documents the final decision in both the Submission Summary and Conclusions sections of the primary review.

4. Primary Review

   The primary review is due by the date indicated in the submission timeline.

   The completed review includes the PR's recommendation: (1) concur with the protocol, (2) do not concur with the protocol, or (3) request an ERA. If the PR recommends an ERA, the review provides the PR's specific comments for the ERA request in the Transmit to Sponsor section of the review. (For definition and scope of an ERA request, please see Appendix 2.)

   The primary review file name contains the submission number and the 3-letter identifier of the review type, followed by ".rev". (Please see Appendix 3 for file-naming conventions.) For example, the review for target animal safety study protocol E0019 is named "E0019tsp.rev".

   The PR notifies the entire project team of the final decision (i.e., protocol concurrence, protocol non-concurrence, or ERA request).

[7] See P&P 1243.3029.

If requesting an ERA, the PR does not return the submission jackets to the DCU at this time. The PR sends the electronic copy of the PR review to the mailbox "CVM ONADE Records" for archiving, but keeps the hardcopies of the PR review and the consulting reviews.[8]

VI. SPONSOR NOTIFICATION [9]

A. Protocol Acceptable

If the protocol is acceptable, that is, we concur with the protocol, we send an email to the sponsor notifying them that we concur with the protocol (NFA Code 078: NOTIFY YES) by Day 50 (Day A). (Use the ONADE "Protocol Concurrence Notification" email template on your computer.[10]) The division director or team leader sends the email via a division mailbox set up for the sole purpose of sending ERA-related emails. The email is addressed to the person who signed the cover letter or as directed by the sponsor, with a cc to the DCU mailbox "CVM_ONADE_NOTICE_DCU".

1. Email Documentation

   Because the protocol concurrence notification email is an electronic letter to the sponsor, the primary review division prints a copy of the email on pink paper for inclusion in the final action package (behind the final action letter) as a stand-alone document, and an electronic copy is saved as described below.

   - The protocol concurrence notification email file name contains the submission number and the 3-letter identifier of the review type,

[8] See P&P 1243.3030.

[9] If we notify the sponsor after Day 50, we miss the ADUFA deadline of 50 days for the non-final action. Although we miss the ADUFA deadline of 50 days for sponsor notification, we continue with the review process. If we concur/non-concur with a protocol, we must first notify the sponsor (as this triggers the new ADUFA deadline for the final action), then issue a protocol concurrence/non-concurrence letter to the sponsor by the ADUFA deadline of Day 60. If we request an ERA, we must receive the ERA within 10 days. If the ERA is not received on time, the ADUFA deadline for the protocol is still 75 days. If the ERA is received on time and acceptable, the ADUFA deadline for the submission is still 20 days after receipt of the ERA, but no later than Day 80.

[10] For more information on how to use ONADE templates for emails and letters, please see the ONADE Tools Manual.

followed by "-notice". (Please see Appendix 3 for file-naming conventions.) For example, the email notification that we concur with target animal safety study protocol E0019 is named "E0019tsp-notice.htm". To save an email in OUTLOOK, click on File/Save As within the opened email, choose the location to which it will be saved, choose the type of file (save as HTML [*.htm]), then click "Save".

The primary review division sends the electronic file of the protocol concurrence notification email to the DCU mailbox "CVM ONADE Records" for archiving.

2. New ADUFA Deadline

The DCU enters the protocol concurrence notification date into STARS when the DCU mailbox "CVM_ONADE_NOTICE_DCU" receives the cc of the notification email. This triggers a new ADUFA deadline of 60 days for the protocol. Please note that the DCU does not generate a new cover sheet for the protocol. Reviewers should refer to the STARS Pending Reviews screens and the submission timeline for the new ADUFA deadline.

The primary review division prepares a final action package using current procedures, and we issue a protocol concurrence letter to the sponsor by Day 60 (FA Code 045: PROT CONCR).[11] (Use the "ProtocolConltr" template on your computer.)

B. Protocol Not Acceptable

If the protocol is not acceptable, that is, we do not concur with the protocol, we send an email to the sponsor notifying them that we do not concur with the protocol (NFA Code 079: NOTIFY NO) by Day 50 (Day A). (Use the ONADE "Protocol Non-concurrence Notification" email template on your computer.) The division director or team leader sends the email via a division mailbox set up for the sole purpose of sending sponsor protocol notifications. The email is addressed to the person who signed the cover letter or as directed by the sponsor, with a cc to the DCU mailbox "CVM_ONADE_NOTICE_DCU".

[11] See P&P 1243.3030.

The email notifying the sponsor that we do not concur with the protocol also provides preliminary broad areas of protocol deficiency, such as statistical methodology, clinical observations, or lack of detail. The protocol non-concurrence letter, which we send by Day 60 (see details below), will provide the detailed protocol assessment.

Note: The protocol non-concurrence notification email cannot have any attachments. All information transmitted to the sponsor must be contained within the body of the email.

1. Email Documentation

   Because the protocol non-concurrence notification email is an electronic letter to the sponsor, the primary review division prints a copy of the email on pink paper for inclusion in the final action package (behind the final action letter) as a stand-alone document, and an electronic copy is saved as described below.

   - The protocol non-concurrence notification email file name contains the submission number and the 3-letter identifier of the review type, followed by "-notice". (Please see Appendix 3 for file-naming conventions.) For example, the email notification that we do not concur with target animal safety study protocol E0019 is named "E0019tsp-notice.htm". To save an email in OUTLOOK, click on File/Save As within the opened email, choose the location to which it will be saved, choose the type of file (save as HTML [*.htm]), then click "Save".

   The primary review division sends the electronic file of the protocol non-concurrence notification email to the DCU Mailbox "CVM ONADE Records" for archiving.

2. New ADUFA Deadline

   The DCU enters the protocol non-concurrence notification date into STARS when the DCU mailbox "CVM_ONADE_NOTICE_DCU" receives the cc of the notification email. This triggers a new ADUFA deadline of 60 days for the protocol. Please note that the DCU does not generate a new cover sheet for the protocol. Reviewers should refer to the STARS Pending Reviews screens and the submission timeline for the new ADUFA deadline.

The primary review division prepares a final action package using current procedures, and we issue a protocol non-concurrence letter by Day 60 (FA Code 046: PROT NCONC). (Use the "ProtocolNonconltr" template on your computer.)

C. ERA Request

If we are requesting an ERA, the PR prepares the ERA request email to the sponsor using the Transmit to Sponsor comments from the primary and consulting reviews. The division director or the team leader sends the ERA request email to the sponsor. (Use the ONADE "Protocol ERA Request" email template on your computer.)

VII. ERA REQUEST

A. ERA Request Email

We send the ERA request via email to the sponsor by Day 50 (Day A). The division director or team leader sends the email via a division mailbox set up for the sole purpose of sending ERA-related email to sponsors. The email is addressed to the person who signed the cover letter or as directed by the sponsor, with a cc to the DCU mailbox "CVM_ONADE_NOTICE_DCU".

Note: The ERA request email cannot have any attachments. All information transmitted to the sponsor must be contained within the body of the email.

The ERA is due within 10 days of the ERA request (Day B).

B. Email Documentation

Because the email is an electronic letter to the sponsor, the primary review division prints a copy of the ERA email on pink paper for inclusion in the final action package (behind the final action letter) as a stand-alone document, and an electronic copy is saved as described below.

- The ERA request email file name contains the submission number and the 3-letter identifier of the review type, followed by "- notice". (Please see Appendix 3 for file-naming conventions.) For example, the ERA request for target animal safety protocol submission E0019 is

named "E0019tsp-notice.htm". To save an email in OUTLOOK, click on File/Save As within the opened email, choose the location to which it will be saved, choose the type of file (save as HTML [*.htm]), then click "Save".

The primary review division sends the electronic file of the ERA request email to the DCU Mailbox "CVM ONADE Records" for archiving.

C. New ADUFA Deadline

The DCU enters the ERA request date into STARS when the DCU mailbox "CVM_ONADE_NOTICE_DCU" receives the cc of the ERA request email. This triggers a new ADUFA deadline of 75 days for the protocol. Please note that the DCU does not generate a new cover sheet for the protocol. Reviewers should refer to the STARS Pending Reviews screens and the submission timeline for the new ADUFA deadline.

VIII. ERA NOT RECEIVED WITHIN 10 DAYS OF ERA REQUEST (BY DAY B)

A. Protocol Non-concurrence

If we do not receive the ERA within 10 days of the ERA request (i.e., by Day B), or the sponsor notifies us that they will not be submitting an ERA, the protocol remains unacceptable and we issue a non-concurrence letter for the protocol.

1. The PR documents that we did not receive the ERA within 10 days of the ERA request in a review. The review is limited to stating that we did not receive the ERA within 10 days of the ERA request, and that we will issue a protocol non-concurrence letter for the submission.

   The title of the review should reflect the type of review written, followed by " - ERA". [12]

   The review file name contains the submission number and the 3-letter identifier of the review type, followed by "-no_era.rev". (Please see Appendix 3 for file-naming conventions.) For example, the review documenting that we did not receive the ERA within 10 days of the request

[12] See P&P 1243.3009.

for target animal safety protocol submission E0019 is named "E0019tsp-no_era.rev".

2. The primary review division prepares a final action package using current procedures, and we issue a protocol non-concurrence letter to the sponsor by Day 75. (Use the ONADE "ERA-ProtocolNonconltr" template on your computer.) The non-concurrence letter should be a copy-and-paste from the ERA request email, which already details the reasons the protocol remains unacceptable.

B. Refuse to Review the ERA if Received Late

If we receive the ERA but it arrives more than 10 days after the ERA request, we do not review it. Because we cannot administratively RTR an amendment (T submission), the DCU automatically logs in the late ERA as a new submission of the parent submission type – in this case, as a protocol (E) submission. We issue an RTR letter to the sponsor for the late ERA/protocol submission. (Use the ONADE "ERA-RTR ltr" template on your computer.)

IX. ERA RECEIVED WITHIN 10 DAYS OF ERA REQUEST (BY DAY B)

A. New ADUFA Deadline

If we receive the requested ERA within 10 days of the ERA request (i.e., by Day B), receipt of the ERA in the DCU (Day C) triggers a new ADUFA deadline for the protocol (Day D), which is Day C plus 20 days.[13] Please note that the DCU does not generate a new cover sheet for the protocol. Reviewers should refer to the STARS Pending Reviews screens and the submission timeline for the new ADUFA deadline.

NOTE: The PR and all consulting reviewers add the date we receive the ERA into the submission timeline so that the timeline accurately reflects all of the due dates.

B. Protocol Changes and Certification

The sponsor should highlight the protocol changes we requested in the ERA, including minor modifications necessary during the incorporation of the requested changes. The sponsor should also provide written certification that, with the

[13] Day D cannot be less than Day 60 or greater than Day 80.

exception of the highlighted protocol changes, the text of the protocol found in the ERA is identical to the text of the original protocol, as amended by any minor amendments prior to the ERA request, and that no other text changes beyond those highlighted have been made. If the sponsor does not highlight protocol changes and/or does not provide written protocol certification, we do not consider the ERA acceptable for review. (Please see Section X below.)

C. Consulting Review Requests

After ascertaining that the sponsor has highlighted and certified the ERA protocol changes, the PR sends out consulting requests for the ERA. The PR should use informed discretion in deciding which consulting reviewers need to review the ERA. Not all reviewers consulted for the original review may need to be consulted for the ERA, but the PR should realize that the information in the submitted ERA might impact a consulting reviewer's original conclusion(s). If there is any question, the PR should discuss the issue with the consulting reviewers.

When sending the consulting requests for the ERA, the PR should also send the jackets from the original protocol submission in case the consulting reviewers need to refer back to the previously reviewed information. The PR should use the existing Review Request and Movement Form to move the jackets back through the DCU to the appropriate consulting reviewer. In the "For Reviewer's Use" box, the PR should write that the jackets are being re-issued to the consulting reviewer for review of an ERA. The DCU will assign the appropriate package indicator (A1, B1, etc.) in the upper right-hand corner of the form.

D. Assessment of ERA

The PR and all consulting reviewers determine whether the ERA is acceptable for review within the timeframe indicated in the submission timeline and as described below.

The PR and the consulting review divisions do an initial assessment of the ERA to determine that (1) it appears to provide information on all the ERA-requested items and (2) it does not provide significant additional information beyond the scope of the ERA request. The ERA has to meet both conditions or it is not acceptable for review. This is a basic screen to determine if the ERA is acceptable for review; it is not a thorough review of the information to determine the acceptability of the protocol.

The consulting reviewers email the PR their conclusions that either (1) the submitted ERA does not address the ERA request, including the reasons why the ERA is not acceptable for review by the consulting reviewer, or (2) the ERA is acceptable for review by the consulting reviewer.

An ERA is not acceptable for review if one or more review groups makes an unacceptable determination after the initial ERA assessment. Therefore, while some review groups may find the ERA acceptable for review from their perspective, we may determine that the ERA is unacceptable for review overall.

An ERA is also not acceptable for review if the protocol changes in the ERA are not highlighted and/or the sponsor has not certified that, with the exception of the highlighted protocol changes, the text of the protocol found in the ERA is identical to the text of the original protocol, as amended by any minor amendments prior to the ERA request, and that no other text changes beyond those highlighted have been made.

X. ERA NOT ACCEPTABLE FOR REVIEW

If the ERA is not acceptable for review, the following actions occur:

A. Consulting Requests Returned

If consulting requests have been sent out, the consulting reviewers return consulting requests for the ERA and the jackets from the original protocol submission to the PR within 5 days of the decision.

B. ERA Converted

We do not review an ERA that is not acceptable for review. Because we cannot administratively RTR an amendment (T submission), the PR converts the ERA to a new submission of the parent submission type using the STARS Correction Request Form. In this case, the PR converts the unacceptable ERA to a protocol (E) submission. We issue an RTR letter to the sponsor for the converted ERA/protocol submission. (Use the ONADE "ERA-RTR ltr" template on your computer.)

C. Protocol Not Acceptable

1. The PR completes a review that cites the unacceptability of the submitted ERA as the basis for not concurring with the protocol. The PR includes the emails from the consulting reviewers in the administrative record.

   The title of the review should reflect the type of review written, followed by " - ERA".

   The review file name contains the submission number and the 3-letter identifier of the review type, followed by "-era.rev". (Please see Appendix 3 for file-naming conventions.) For example, the review documenting that the ERA for target animal safety protocol submission E0019 was unacceptable is named "E0019tsp-era.rev".

2. The primary review division prepares a final action package using current procedures, and we issue a protocol non-concurrence letter to the sponsor by Day 75. (Use the "ERA-ProtocolNonconltr" template on your computer.) The non-concurrence letter should be a copy-and-paste from the ERA request email, which already details the reasons the protocol remains unacceptable.

XI. ERA ACCEPTABLE FOR REVIEW

If the ERA is acceptable for review, the PR and the consulting reviewers review the ERA. There is only one ERA allowed for a submission; we cannot request any subsequent ERAs during review of the submission. Additional minor amendments are allowed.

A. Consulting Reviews

ERA consulting reviews are due by the date indicated in the submission timeline.

The ERA consulting review does not encompass the entire protocol; that is, it does not re-review the information originally submitted. The ERA review will incorporate this information by referencing the previous consulting review. The ERA consulting review is limited to a review of the submitted ERA. The review should determine whether the ERA gives us the information needed to concur with the protocol.

The completed review includes the consulting reviewer's recommendation: (1) concur with the protocol or (2) do not concur with the protocol. If alternative methods of review are utilized (i.e., meeting among team members to determine concurrence or non-concurrence), the PR will document the consulting reviewers' protocol concurrence.[14]

The title of the review should reflect the type of review written, followed by " - ERA".

The ERA consulting review file name contains the submission number and the alphanumeric designation of the consulting review, followed by "-era.rev". (Please see Appendix 3 for file-naming conventions.) For example, the biometrics D1 consulting review of the ERA for protocol submission E0019 is named "E0019d1b-era.rev".

Return the consulting review and jackets from the original protocol submission to the PR using current procedures.

B. Outcome of ERA Review

The PR, in consultation with their team leader and the consulting reviewers as needed, evaluates the recommendations from the primary ERA review and all consulting ERA reviews to determine the appropriate final action: (1) concur with the protocol or (2) do not concur with the protocol. The PR documents the final decision in both the Submission Summary and Conclusions sections of the primary review.

C. Primary Review

The primary review of the ERA is due by the date indicated in the submission timeline.

The primary ERA review does not encompass the entire protocol; that is, it does not re-review the information originally submitted. The ERA review will incorporate this information by referencing the previous review. The ERA review will be limited to a review of the submitted ERA. The review should determine whether the ERA gives us the information needed to concur with the protocol.

[14] See P&P 1243.3025.

The completed review includes the PR's recommendation: (1) concur with the protocol or (2) do not concur with the protocol.

The title of the review should reflect the type of review written, followed by " - ERA".

The review file name contains the submission number and the 3-letter identifier of the review type, followed by "-era.rev". (Please see Appendix 3 for file-naming conventions.) For example, the review of the ERA for target animal safety study protocol submission E0019 is named "E0019tsp-era.rev".

XII. PROTOCOL FINAL ACTION AFTER ERA REVIEW (BY DAY D)

There are two possible final actions for the protocol:

A. Protocol Acceptable

If the protocol is acceptable after submission of the ERA, the primary review division prepares a final action package using current procedures, and we issue a protocol concurrence letter to the sponsor by Day D (ERA received date plus 20 days). (Use the "ProtocolConltr" template on your computer.)

- FA - Protocol Acceptable as Submitted; Letter Sent (FA Code 045: PROT CONCR)

B. Protocol Not Acceptable

If the protocol remains unacceptable after submission of the ERA, the primary review division prepares a final action package using current procedures, and we issue a protocol non-concurrence letter to the sponsor by Day D (ERA received date plus 20 days). (Use the "ProtocolNonconltr" template on your computer.)

- FA – Protocol Not Acceptable as Submitted; Letter Sent (FA Code 046: PROT NCONC)

XIII. REFERENCES

ADUFA II Goals Letter

CVM Guidance for Industry

How the Center for Veterinary Medicine Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug (#119)

CVM Program Policy and Procedures Manual

1243.2050 – Refuse to file and refuse to review

1243.3009 – Format and style conventions for reviews and submission summaries

1243.3025 – Preparing a memorandum of conference (MOC)

1243.3026 – Amending STARS submissions

1243.3029 – Closing out a consulting review for STARS submissions

1243.3030 – Completing final action packages for STARS submissions

1243.4060 – Review of protocols

XIV. VERSION HISTORY

September 19, 2008 – original version

APPENDIX 1. ADUFA II GOALS LETTER LANGUAGE – PROTOCOLS

7. Investigational Animal Drug Protocol without Data Submissions

a. The Agency will review and act on 90 percent of investigational animal drug submissions consisting of protocols without substantial data, that the Agency and the sponsor consider to be an essential part of the basis for making the decision to approve or not approve an animal drug application or supplemental animal drug application, within

i. 60 days after the submission date (Day 60) if the Agency does not request an end-review amendment to the protocol.

(1) If the Agency determines that the protocol is acceptable, the Agency will notify the sponsor of this decision electronically on or before Day 50, followed by a complete action letter; or

(2) If the Agency determines that a protocol is not acceptable, the Agency will notify the sponsor of this decision electronically, providing preliminary broad areas of protocol deficiency, on or before Day 50, with the subsequently issued complete action letter providing the detailed protocol assessment. The sponsor may contact the Agency for a brief clarification of these areas of deficiency prior to the issuance of the complete action letter; or

ii. 75 days after the submission date if the Agency electronically requests an end-review amendment to the protocol on or before Day 50, but the sponsor fails to submit such amendment within 10 days of the amendment request date. If a sponsor files an amendment more than 10 days after the amendment request date, then the amendment is ineligible for consideration as an end-review amendment, the extended performance goal (refer to 7.a.iii below) will not apply, and a complete action letter will be issued by Day 75 for the original submission; or

iii. the greater of 60 days after the original protocol is received by the Agency or 20 days after the amended protocol is received by the Agency if the Agency electronically requests an end-review amendment on or

before Day 50 and the sponsor submits such amendment within 10 days of the date the amendment is requested.

b. Sponsors are not required to submit study protocols for review. However, for each voluntarily submitted protocol for a study that the Agency and the sponsor consider to be an essential part of the basis for making the decision to approve or not approve an animal drug application or supplemental animal drug application, the Agency will issue a complete action letter providing comments resulting from a complete review of the protocol. The complete action letter will be as detailed as possible considering the quality and level of detail of the protocol submission; will include a succinct assessment of the protocol; and will state whether the Agency agrees, disagrees, or lacks sufficient information to reach a decision that the protocol design, execution plans, and data analyses are adequate to achieve the objectives of the study.

c. If the Agency determines that a protocol is acceptable, this represents an agreement that the data generated by the protocol can be used to support a safety or effectiveness decision regarding the subject animal drug. The fundamental agreement is that having agreed to the design, execution, or analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspectives on the issues of design, execution, or analyses unless the Agency by written order determines that a substantiated scientific requirement essential to the assessment of the study appeared after the Agency's protocol assessment, or public or animal health concerns unrecognized at the time of protocol assessment under this process are evident.

d. The end-review amendment procedure is not intended to prevent the use of minor amendments during Agency review of a protocol without data submission ….

APPENDIX 2. DEFINITION AND SCOPE OF ERA REQUESTS

CVM proposed the ERA process during ADUFA II negotiations, in response to discussions on multiple review cycles. CVM made a good faith commitment to use this ERA process, when possible, with the goal of obtaining a complete review decision in one cycle.

Sponsors are expected to submit high quality submissions to facilitate review by the Office of New Animal Drug Evaluation (ONADE). Reviewers should follow the policies regarding Refuse to File and Refuse to Review to determine if a submission can reasonably be reviewed. Once ONADE determines that a submission is acceptable for filing or review, both the minor amendment and ERA tools are available for use to facilitate completing the submission.

Reviewers should follow the policies regarding minor amendments during the course of their review. Examples of minor amendments are found in P&P 1243.3030.

Reviewers should communicate with sponsors as needed during the review process to obtain clarification or other information to facilitate the review.

Reviewers should consider all of the following factors in the decision to request an ERA. Request an ERA if:

- We can clearly identify and communicate to the sponsor the changes and/or submission of additional information that can complete the submission.
- We can complete review of the ERA submission and make the review decision in the time allotted. This decision should be based solely on the nature of the required changes/additional information.
- All consulting reviews and the primary review, when taken as a whole, support the decision to request the ERA.

APPENDIX 3. FILE-NAMING CONVENTIONS

Table 1. Protocol review types and their 3-letter file identifiers

Review Type	3-Letter File Identification
Bioequivalence	bqp
Combination Effectiveness and Safety	esp
Effectiveness	efp
Human Food Safety – Analytical Methods	hsa
Human Food Safety – Genetox	hsg
Human Food Safety – Microbiological	hsm
Human Food Safety – Residue	hsr
Human Food Safety – Toxicology	hst
Human Safety – User Safety	hsu
Manufacturing	mfp
Pharmacokinetic	pkp
Target Animal Safety	tsp

Table 2. Era-related documents and their file identifiers

Document Type	File identifier after submission ID
Initial review	None
Sponsor notification email	-notice
ERA-related protocol reviews:	
No ERA submitted	-no_era
ERA submitted (both ERA not acceptable and ERA acceptable)	-era