

Providing Lot Release Protocol Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to <https://www.regulations.gov/>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-1998-D-0095 (formerly docket number 1998D-0315).

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010 or email at ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2019

Contains Nonbinding Recommendations

Table of Contents

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. DISCUSSION 2

A. Format for Electronic Lot Release Protocol Submissions..... 3

 1. Hypertext Links and Bookmarks 3

 2. Electronic Lot Release Protocol Signature Letter..... 4

 3. Naming the Electronic Lot Release Protocol File..... 4

B. Electronic Lot Release Protocol Submissions Through FDA’s Electronic Submissions Gateway 4

 1. Preparatory Steps for Using the ESG..... 5

 2. Procedures Following the Completion of the Preparatory Steps 6

 3. Help and Information 7

C. Electronic Lot Release Protocol Submissions on CD-ROM 8

 1. Labeling the CD-ROM 8

 2. Packaging and Shipping..... 8

 3. Delivery Address 9

D. Feedback on Your Electronic Lot Release Protocol Submission..... 9

E. Shipping Samples to FDA When Using the ESG to Submit the Associated Lot Release Protocols..... 9

APPENDIX 1: EXAMPLE OF A TABLE OF CONTENTS WITH BOOKMARKS FOR AN ELECTRONIC LOT RELEASE PROTOCOL 10

APPENDIX 2: EXAMPLES OF CD-ROM LABELS 11

APPENDIX 3: CHECKLIST PRIOR TO SUBMITTING AN ELECTRONIC LOT RELEASE PROTOCOL 12

Providing Lot Release Protocol Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, the Center for Biologics Evaluation and Research (CBER), within the U.S. Food and Drug Administration (FDA, the agency, or we), are issuing this guidance under Title 21 of the Code of Federal Regulations (CFR) 601.14(a) to assist you, manufacturers of biological products regulated by CBER,¹ in submitting lot release protocols in electronic format to CBER's Product Release Branch, within the Office of Compliance and Biologics Quality (OCBQ). This guidance updates and supersedes the similarly named guidance, "Guidance for Industry, Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format - Lot Release Protocols," dated November 2007 (2007 guidance). We are updating this guidance to include the submission of electronic lot release protocols through the FDA's Electronic Submissions Gateway (ESG).²

In the Federal Register of December 8, 1995 (60 FR 63048),³ we announced that we no longer require routine lot-by-lot release for specified categories of biological products subject to licensure, previously referred to as well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products (see 21 CFR 601.2(c)). This guidance is not intended to modify that document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidance means that something is suggested or recommended but not required.

¹ Although most lot release protocols and products that are submitted for the lot release program are regulated by CBER, the program also receives a small number of lot release protocols for products that are regulated by the Center for Drug Evaluation and Research (CDER).

² For general information about regulatory submissions in electronic format for biological products, see <https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/ucm163685.htm>.

³ Federal Register notice entitled "Interim Definition and Elimination of Lot-by-Lot Release for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products."

Contains Nonbinding Recommendations

II. BACKGROUND

The ESG is an agency-wide solution for accepting electronic regulatory submissions. The ESG enables the secure submission of premarket and postmarket regulatory information to FDA for review. It is the central transmission point for sending secure information electronically to the agency. Within that context, the ESG is a conduit along which submissions travel to reach the proper FDA Center or Office.

Lot release is a system that permits FDA to verify product quality through protocol review and sample testing of many biological products that we regulate. In accordance with 21 CFR 610.2(a), CBER may require you to submit for CBER review and confirmatory testing samples of any lot of any licensed product, together with the protocols showing results of applicable tests when deemed necessary for the safety, purity, or potency of the product.

III. DISCUSSION

Submission of your lot release protocol submissions, consistent with lot release requirements applicable to your product, in an electronic format that is readily accessible will facilitate our review of your submission.

FDA has encouraged applicants to submit lot release protocols electronically through the ESG since 2009. This guidance is being updated to provide information on using the ESG. It includes a high-level description of the procedures that are necessary for manufacturers to use the ESG to submit lot release protocols to CBER; however, we also refer manufacturers to various website links for more detailed information on using the ESG for this purpose. The information available on our website is updated periodically.

Pursuant to 21 CFR 11.2(b)(2), FDA has identified lot release protocols as one of several submission types described in Public Docket 1992S-0251 that the agency accepts in electronic format. We encourage the use of FDA's ESG for submitting electronic lot release protocols to CBER because it facilitates our ability to receive and review these submissions. If manufacturers are not able to provide these submissions to us using the ESG, manufacturers may use other means to submit their lot release protocols to the agency, such as mailing a compact disc read-only memory (CD-ROM⁴).⁵ This guidance is intended to provide you with

⁴ CBER's Product Release Branch accepts lot release protocol submissions on digital video disc or digital versatile disc (DVDs) in addition to CD-ROMs. The submission process for DVDs is identical to the submission process for CD-ROMs that is described in this guidance.

⁵ We discourage the submission of lot release protocols in paper format, but we continue to accept these submissions when firms are not able to submit their lot release protocols electronically.

Contains Nonbinding Recommendations

recommendations for submitting lot release protocols showing results of applicable tests in an electronic format, as provided in 21 CFR Part 11.⁶

A secure email account should be established with FDA to protect proprietary and confidential information and to facilitate communication. A secure email address allows for encrypted exchange between the manufacturer and the agency, for example, about your electronic lot release protocol.⁷ CBER-generated email regulatory communication will only be sent via secure email.⁸ For information on how to establish a secure email account with CBER, you may contact the agency at SecureEmail@fda.hhs.gov.

A. Format for Electronic Lot Release Protocol Submissions

Manufacturers should submit their lot release protocols in a portable document format (PDF) file when transmitting electronically to CBER's Product Release Branch. We request this format when submitting electronically through the ESG as well as when submitting electronically by CD-ROM. The lot release protocol PDF file should be placed in an electronic folder, and the folder name should be the 6-digit submission tracking number (STN).⁹ Manufacturers who are currently submitting their lot release protocols to CBER using a paper format should only need minor modifications for the conversion to PDF. The PDF version should be full-text searchable and not simply a static scan of the entire paper protocol. We recommend that you do not use the security option and passwords for the submission, as these could make it difficult for us to access your data. You may send an email message to the Product Release Branch at CBERLotRelease@fda.hhs.gov to receive a lot release protocol template.

1. Hypertext Links and Bookmarks

Lot release protocols vary in length, depending on the specific content. We recommend that you use functional bookmarks or a hypertext linked Table of Contents to facilitate navigating the protocol, especially for larger ones. An example of a Table of Contents with bookmarks is provided in Appendix 1 at the end of this guidance.

⁶ FDA issued a "Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application," dated August 2003 (September 5, 2003, 68 FR 52779), describing a policy of enforcement discretion relating to certain Part 11 requirements (see

<https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm>). We update guidance periodically. To ensure that you have the most recent version of a guidance, check the FDA Drugs guidance webpage at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁷ Electronic lot release protocols should not be emailed to the agency.

⁸ See FDA "SOPP 8119: Use of Email For Regulatory Communications," Version 3, dated October 1, 2018, at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Procedures/OPPs/UCM585760.pdf>.

⁹ For allergenic products that use the second level STN to identify the product, you should use the primary and secondary level numbers, separated by an underscore, as the folder name.

Contains Nonbinding Recommendations

2. Electronic Lot Release Protocol Signature Letter

For purpose of signing the lot release protocol in PDF, you should use the electronic lot release protocol (e-LRP) Signature Letter, which includes information about your company and the lot release protocol that you are submitting.¹⁰ The e-LRP Signature Letter should be included as the first page of the lot release protocol PDF file.¹¹ You may send an email message to the Product Release Branch at CBERLotRelease@fda.hhs.gov to receive information on the latest e-LRP Signature Letter template to use.

3. Naming the Electronic Lot Release Protocol File

The e-LRP, in PDF, must be assigned a unique filename for each product lot. The filename is composed of alphanumeric characters. You should not use any special characters in the filename. The first four numbers represent the year of the submission (e.g., 2018). The next four numbers represent the sequential lot submitted for that year (e.g., 0001, 0002, 0003, etc.), and these 8 numbers are followed by a dot. The final two to three alphanumeric characters represent the type of submission (.P0 (zero) specifies an original protocol, and .PC specifies a corrected protocol). Thus, 20180003.P0 represents the original protocol for the third lot submitted in the year 2018.

A corrected lot release protocol is a submission to correct minor clerical or transcription errors or to clarify lot release information in response to questions by FDA. For submissions under a corrected lot release protocol, designate each corrected protocol using “.PC,” followed by the correction number (i.e., .PC1 represents the first corrected protocol, .PC2 represents the second corrected protocol, etc.). Thus, 20180003.PC1 represents the first correction of the original protocol for the third lot submitted in the year 2018.

B. Electronic Lot Release Protocol Submissions Through FDA’s Electronic Submissions Gateway

Currently, our preferred method of transmitting lot release protocols is through FDA’s ESG. The FDA’s ESG provides a single point of entry for receiving and processing all electronic submissions in a highly secure environment. It complies with secure Hypertext Transfer Protocol (HTTP) messaging standards and uses digital certificates for secure communication. The electronic submission process through the ESG encompasses the receipt, acknowledgment of receipt (to the sender), routing, and notification (to a receiving FDA Center or Office) of an electronic submission.

Manufacturers have two options for sending submissions through the ESG to the agency: WebTrader or Applicability Statement 2 (AS2).

¹⁰ The authorized official noted on the first page of the electronic lot release protocol should be the same person who signs the e-LRP Signature Letter.

¹¹ The signed e-LRP Signature Letter portion of the PDF file does not need to be text searchable.

Contains Nonbinding Recommendations

WebTrader is a Web interface designed for low volume submitters and is likely the most appropriate method for manufacturers who want to submit lot release protocols to the agency. This web-based interface, which involves installing software on the submitter's computer, is used to send documents and receive receipts and acknowledgments from FDA. The WebTrader application makes communication with FDA simple, cost-effective, and time-independent. WebTrader requires each user from an industry partner to register for his or her own unique WebTrader account.

AS2 is a system-to-system connection (also referred to as a "server-to-server" or "gateway-to-gateway" connection) to exchange information with FDA. AS2 requires a gateway software implementation on the submitter's end, requiring a server(s) and software procurement and configuration. AS2 provides an automated connection to FDA for submissions, receipts, and acknowledgments. System-to-system communication requires one user from an organization to register for the organizational account.

The [ESG User Guide](#), available on our website,¹² provides manufacturers with an overview of the ESG registration process, the preparatory steps that are necessary for establishing an ESG account, and the specific steps that are necessary for establishing a WebTrader (Web interface) ESG account,¹³ in addition to other resources. The User Guide explains how to send documents through the ESG, including the creation of test and production accounts. We recommend that manufacturers refer to the ESG User Guide and the additional links that are on our ESG webpage for current and complete information on how to use the ESG.¹⁴

There are several preparatory steps that are needed prior to beginning the ESG registration process. In this guidance, we provide a high-level overview of these preparatory steps. Considerations for each preparatory step are covered in more detail in the ESG User Guide.

1. Preparatory Steps for Using the ESG

- a. Send an Email Message to the ESG Help Desk

Send an email message to ESGHelpDesk@fda.hhs.gov, indicating that you would like to register for an ESG account.

- b. Submit a Letter of Non-Repudiation Agreement

The non-repudiation agreement allows FDA to receive electronically signed submissions in compliance with 21 CFR 11.100.

¹² See <https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm334359.htm> for the ESG User Guide.

¹³ The ESG User Guide also includes information for establishing an AS2 ESG account.

¹⁴ See <https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm> for general information on the ESG.

Contains Nonbinding Recommendations

c. Obtain a Digital Certificate

Digital certificates ensure private and secure submission of electronic documents. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents.

d. Understand the Submission Guidelines, Including File Naming Conventions

The guidelines for preparing lot release protocol submissions are described in section III.A. of this guidance.

e. Determine the Submission Method

Manufacturers who want to submit lot release protocols can use the ESG Web Interface by creating a WebTrader account or using an AS2 gateway-to-gateway account. WebTrader is designed for low-volume submitters and is likely the most appropriate method for manufacturers who want to submit lot release protocols to the agency.

f. Review and Ensure that the Connection Requirements for the Selected Submission Method Are Met

The ESG User Guide lists the requirements for each method, including Web browsers, software, disk space, and connection speed.

2. Procedures Following the Completion of the Preparatory Steps

After completing the preparatory steps, manufacturers may consult the [ESG User Guide](#) for the steps that are necessary to submit lot release protocols through the ESG by establishing a WebTrader account (Chapter 4), or an AS2 connection (Chapter 5). The following steps are necessary to establish an ESG production account for submitting your lot release protocols to CBER through the ESG:¹⁵

a. Obtain Access to the Electronic Submissions Gateway

The ESG User Guide explains how to set up a test account and a production account. Once a test account is approved and set up for a WebTrader account, a profile will need to be established for each individual who will need access. For example, if more than one person will be submitting electronic lot release protocols from the same

¹⁵ We provide a high-level summary of the steps that are necessary to establish an ESG production account in this guidance. We recommend that manufacturers consult the [ESG User Guide](#) and the additional information that we have on our [ESG webpage](#) for a more detailed description.

Contains Nonbinding Recommendations

manufacturing facility, each person will need to create his or her own profile and send a test submission.

b. Send a Test Submission Through the ESG

To receive an ESG production account, which permits manufacturers to submit lot release protocols through the ESG, manufacturers should first successfully submit a lot release protocol test submission that is formatted as described in section III.A. of this guidance. You may use a previously submitted lot release protocol in PDF as your test submission.

Lot release protocol PDF files should be placed in an electronic folder prior to sending them through the ESG, and the folder name should be the 6-digit STN. Placing the lot release protocol PDF file in a folder prior to sending it through the ESG helps to ensure that the filename is maintained.

For WebTrader accounts, each individual who establishes a profile should send one test submission through the ESG. The same test submission may be used by multiple individuals.

c. ESG Notification

The ESG system will immediately notify you when your test submission has been successfully received through the ESG. If you do not receive a successful transmission notification, contact the ESG Help Desk at ESGHelpDesk@fda.hhs.gov and inform them that you have not received a communication indicating that the transmission was received.

d. Feedback on the ESG Test Submission

Manufacturers should send an email message to CBER's Product Release Branch at CBERLotRelease@fda.hhs.gov after sending the test submission to ensure that the Branch has received it. When the Product Release Branch successfully receives your test submission and confirms that it is in the proper format, you will be notified by ESG Help Desk personnel that your access has been upgraded to an ESG production account. You may then proceed to send your lot release protocols to CBER through the ESG.

3. Help and Information

If you need assistance with establishing an ESG account or using your ESG production account, you may send an email message to FDA's ESG Help Desk at ESGHelpDesk@fda.hhs.gov.

Contains Nonbinding Recommendations

If you have questions for CBER, regarding submission standards and formatting, you may send an email message to CBER Electronic Submissions (ESUB) at esubprep@fda.hhs.gov.

C. Electronic Lot Release Protocol Submissions on CD-ROM

If manufacturers are not able to submit lot release protocol files through the ESG, you may submit your electronic files on CD-ROM as an alternative to our preferred method. Creation and file naming of an electronic lot release protocol in a PDF file for submitting on a CD-ROM involves the same procedures as those for creating an electronic lot release protocol for submitting through the ESG (see section III.A. of this guidance).

1. Labeling the CD-ROM

You should label your CD-ROM and CD-ROM case to identify your submission with the following information:

- a. Manufacturer name;
- b. Date of submission in the format of DD-MMM-YYYY, with DD and YYYY being numerical and MMM being the first three letters of the month (e.g., “AUG” for August);
- c. STN, license number, and type of lot (“FC” for final container, “B” for bulk, “C” for Concentrated);
- d. Electronic lot release protocol filename(s); and
- e. Lot number(s).

We provide examples of labeled CD-ROMs and their corresponding CD-ROM cases in Appendix 2 at the end of this guidance. We recommend that you label your CD-ROM in a manner that does not interfere with data retrieval.

2. Packaging and Shipping

CD-ROMs should be packaged carefully to ensure that they arrive in a usable condition. CD-ROM cases are less vulnerable when shipped in envelopes with bubble-type protective material or stiff backing. Mailing envelopes padded with paper material, only, typically do not provide adequate protection for shipping CD-ROMs.

Contains Nonbinding Recommendations

3. Delivery Address

CD-ROMs should be sent to the address below. If you are sending lot release samples along with your CD-ROM, you must use a courier service (see 21 CFR 600.2(c)).

Food and Drug Administration
Center for Biologics Evaluation and Research
Sample Custodian
10903 New Hampshire Avenue
WO75-G707
Silver Spring, MD 20993-0002

D. Feedback on Your Electronic Lot Release Protocol Submission

A checklist to help ensure that your electronic lot release protocol is in the proper format prior to submitting it to CBER is provided in Appendix 3 at the end of this guidance. Once your lot release protocol in electronic format has been received and reviewed by the Product Release Branch, the Branch staff will contact you if your submission is not in the proper format. Modifications or resubmissions may be needed, particularly for your initial electronic lot release protocol submission, and we will work with you to ensure an adequate submission.

E. Shipping Samples to FDA When Using the ESG to Submit the Associated Lot Release Protocols

Often lot samples are submitted well before the lot release protocol, while the lot is still in release testing by the manufacturer, to help facilitate sample processing and CBER concurrent testing. If you submit lot samples while release testing is ongoing, you should include a concurrent testing letter along with your samples. You may send an email message to the Product Release Branch at CBERLotRelease@fda.hhs.gov to receive the latest template for the appropriate Concurrent Testing Letter (the Concurrent Testing Letter for general use or the Concurrent Testing Letter for test kits).

Contains Nonbinding Recommendations

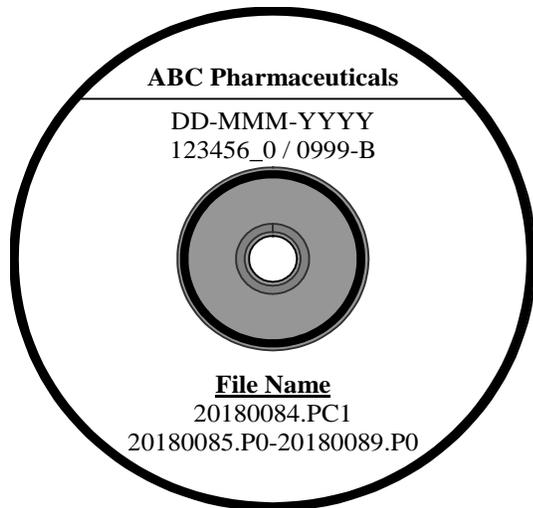
APPENDIX 1: EXAMPLE OF A TABLE OF CONTENTS WITH BOOKMARKS FOR AN ELECTRONIC LOT RELEASE PROTOCOL

1. STN/License No./Type of Lot [Bulk, Final Container, Concentrated]
2. Lot Number
3. Proper Name of Product
4. Firm Name and Address
5. Reason for Submission
6. Test Result Pass Statement
7. Signature Block
8. Electronic Protocol: 20180001.P0
9. Test Results
 - a. Potency
 - b. Specific Activity
 - c. pH
 - d. Moisture
 - e. Total Protein
 - f. Solubility
 - g. Sterility
 - i. Sterility Bulk
 - ii. Sterility Final Container
 - h. Purity
 - i. Limulus Amoebocyte Lysate (LAL)
 - ii. Pyrogen
 - i. Laser Densitometer (LD) Scan
 - i. LD Scan
 - ii. LD Scan Reference

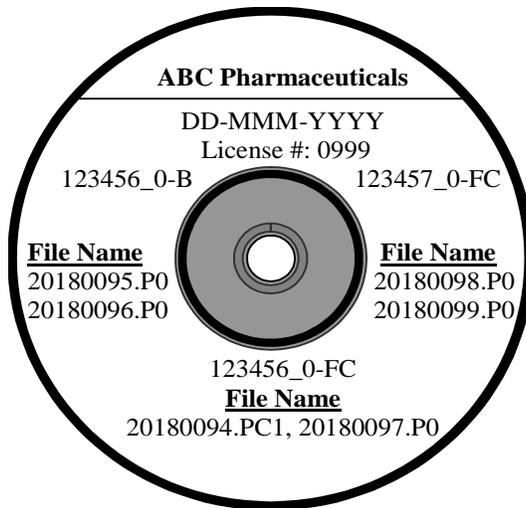
Contains Nonbinding Recommendations

APPENDIX 2: EXAMPLES OF CD-ROM LABELS

A) Single Product Submission



B) Multiple Product Submission



C) CD Case for Disc A

| <u>0999 ABC Pharmaceuticals</u> | |
|---------------------------------|--------------|
| DD-MMM-YYYY | |
| 123456_0-B | |
| Lot # | Filename |
| 8799795A | 20180084.PC1 |
| 8799989B | 20180085.P0 |
| 9567428C | 20180087.P0 |
| 9567428D | 20180088.P0 |
| 9567429K | 20189989.P0 |

D) CD Case for Disc B

| <u>0999 ABC Pharmaceuticals</u> | | |
|---------------------------------|----------|--------------|
| DD-MMM-YYYY | | |
| STN | Lot # | Filename |
| 123456_0-B | 8899989B | 20180095.P0 |
| 123456_0-B | 8899995A | 20180096.P0 |
| 123456_0-FC | 9567415B | 20180094.PC1 |
| 123456_0-FC | 9567418C | 20180097.P0 |
| 123457_0-FC | 9567418D | 20180098.P0 |
| 123457_0-FC | 9567419K | 20180099.P0 |

Contains Nonbinding Recommendations

APPENDIX 3: CHECKLIST PRIOR TO SUBMITTING AN ELECTRONIC LOT RELEASE PROTOCOL

- Confirm that the e-LRP Signature Letter is the first page of the electronic lot release protocol PDF file
- Confirm that the authorized official noted on the first page of the electronic lot release protocol is the same person who signs the e-LRP Signature Letter
- Confirm that the file name for the electronic lot release protocol is in the correct format (see section III.A.3. of this guidance)
- Confirm that the folder name is correct (see section III.A. of this guidance)
- Confirm that the “reason for submission” section is on the first page of the electronic lot release protocol and on the e-LRP Signature Letter
- Confirm that the appropriate box for the “reason for submission” is marked
- Confirm that your entire electronic lot release protocol is text-searchable
- Confirm that your electronic lot release protocol file is virus-free