 Guidance for Industry

Electronic Submission of Lot Distribution Reports for Biological Products

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 written comments at any time to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with Docket Number FDA-2010-D-0205.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.
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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides you, licensed manufacturers of biological products, with recommendations on how to electronically submit lot distribution reports (LDRs) for biological products to the Center for Biological Evaluation and Research (CBER) in a format FDA can process, review, and archive. We, CBER, have developed this guidance after evaluating the results from a pilot project on electronic submission of LDRs.1

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Historically, CBER has received LDRs as paper submissions from manufacturers. We are issuing this guidance to assist manufacturers interested in electronic submissions. We believe that use of a consistent electronic format for LDRs will:

- Eliminate the time and costs associated both with submitting paper reports (for industry) and with converting data from paper reports into electronic format for review and analysis (for FDA);
- Expedite FDA’s access to safety information in a format that would support more efficient and comprehensive reviews; and

1 The capability to receive electronically submitted LDRs is not currently available for therapeutic biological products regulated by the Center for Drug Evaluation and Research (CDER). For a list of these products see: http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm.
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- Enhance FDA’s ability to rapidly communicate information about suspected problems to health care providers, consumers, applicants, and manufacturers within the United States (U.S.) and internationally, in support of FDA’s public health mission.

FDA has worked with industry on electronic submission of postmarketing information. Although establishing a uniform electronic reporting format initially requires additional effort by both FDA and industry, experience has shown that such electronic data submissions enhance efficiency and facilitate the review process. For example, we have found that having an established electronic reporting format allows us to receive standardized and consistent LDR files that can be automatically validated against CBER’s Regulatory Management System-Biologics License Application (RMS-BLA).

RMS-BLA is an information system that CBER uses to track BLAs. CBER’s database for LDRs can link with the RMS-BLA database for such purposes as verifying that CBER has received required LDRs. Furthermore, electronic linkages between CBER’s lot distribution database and CBER’s Adverse Event Reporting System (AERS) and Vaccine Adverse Event Reporting System (VAERS) databases will allow for better monitoring for safety patterns by product lot. Currently, invalid lot identifiers (“lot numbers”) in AERS and VAERS data interfere with such monitoring by reducing available information on actual lots and by distorting data patterns with the “noise” from invalid lots. If AERS or VAERS data entry personnel receive an alert when they enter invalid lot identifiers (that is, when a software look-up function fails to recognize a character string as a valid lot identifier for the corresponding vaccine product), then the data entry clerks can re-examine the source documents and correct the entries for handwriting interpretation or typographic errors. When such corrections are not possible, records can then be flagged as invalid (or not validated) to allow for their exclusion from analyses when only lot data known to be valid will be helpful.

In accordance with ongoing FDA initiatives to encourage the widest possible use of electronic technology, FDA published the proposed rule “Postmarketing Safety Reports for Human Drug and Biological Products; Electronic Submission Requirements” (74 FR 42184) (Aug, 21, 2009) that would, among other things, amend 21 CFR 600.81 to require the electronic submission of LDRs. When the proposed rulemaking becomes final, we may revise, update, or withdraw this guidance document, as appropriate.

III. LOT DISTRIBUTION REPORTS

Currently, under 21 CFR 600.81, licensed manufacturers of biological products must submit to CBER or CDER, as appropriate, LDRs containing certain specified information every 6 months about the quantity of the products distributed under BLAs (including to distributors). As needed, FDA may require a licensed manufacturer to submit more detailed product distribution information. Furthermore, upon written notice, we may request distribution reports at times other than every 6 months.\(^2\)

\(^2\) As currently drafted, the proposed rulemaking described above would not change the content of an LDR but, as a general matter, would require LDRs to be submitted in an electronic format that FDA could process, review, and
Presently, CBER allows you to submit LDRs in electronic format by sending the reports to FDA either: (1) on physical media; or (2) through FDA’s Electronic Submission Gateway (ESG). Currently, there are two acceptable electronic file formats that you may use: (1) American Standard Code for Information Interchange (ASCII); or (2) Extensible Markup Language (XML).  

You should include the following information in your electronic LDRs for each final container lot distributed during the reporting period:

- FDA registered Folder ID (primary Submission Tracking Number (STN));
- FDA registered product and trade name;
- Bulk lot identifier (lot identifiers are often referred to as “lot numbers,” but the character; strings can include letters as well as digits.);
- Fill lot identifier (intermediary between bulk and final container lots);
- Final container lot identifier;
- Distributed number of final dosage containers (e.g., 50,000 10-ml vials);
- Expiration date;
- Initial distribution date4;
- Returned amount of a final container lot; and
- Reporting period start and end dates.

You should include information on product lots intended for “domestic” distribution, i.e., distribution within the U.S. or to U.S. military bases abroad. You need not include information about lots intended for distribution to other countries. However, we retain a field to distinguish between domestic and foreign distribution for consistency with previous file formats and for potential future use if special circumstances should warrant tracking of non-domestic lots distributed.

Although FDA recognizes that details of each manufacturer’s database can differ, there are general steps that every organization should follow in preparing compliant files for electronic submission. For example, manufacturers should “map” (i.e., configure) their output data to the specifications for the file and data layout. Instructions for mapping have not been included in this guidance document, since the procedure depends on the structure and content of each manufacturer’s database. For detailed instructions, please search on CBER’s website for Lot Distribution Data Electronic Submission.

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3 FDA currently expects that in the future, all electronic submissions to the agency will be sent through the ESG and that use of physical media for such submissions eventually will be phased out (74 FR 42189 at n19).

4 The initial distribution date for a final container lot refers to the first time that the lot has been distributed. If a submission is describing distribution of lots in a reporting period from, for example, January 1 of a particular year through June 30 of that year, then lots that had also been distributed in previous periods would still have their original initial distribution dates, which would precede the beginning of this reporting period.
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Where feasible, parameter values for each field should be drawn from FDA’s electronic data standards for Structured Product Labeling (SPL) Resources. The most current information on these electronic data standards is located at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The two files most pertinent for LDRs in SPL (with links to their most current versions) are:

- **Units of Measure**
- **Units of Presentation**

National Cancer Institute (NCI) Thesaurus Object Identifier Definition (OID):
2.16.840.1.113883.3.26.1.1

NCI concept code for potency units: C48470

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm168397.htm (units of measure)

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162049.htm (units of presentation)

If an appropriate value does not appear to meet the needs for a particular product, you should submit a request for additional values to spl@fda.hhs.gov.

IV. VALIDATION

When the LDR has been submitted to CBER, the receiving software completes assimilation of your submission, and you should receive an automated email with summarizing information, such as:

- Company name
- Submitter email address
- Primary STN (folder id)
- Product name
- Trade name
- Total of doses distributed per product
- Current reporting period data and
- Cumulative totals for the previous 3 years (based on data previously reported)

Upon receipt of the automated email, you should verify the integrity of the transmission within 15 calendar days. If any correction is necessary or questions arise, you should call 301-827-9426 or 301-827-5218, or communicate via email to LDD@fda.hhs.gov.

V. ESG SERVICE INTERRUPTIONS

Temporary service interruptions in the ESG will automatically extend submission deadlines until 24 hours after restoration of full operations. Furthermore, if your system has technical difficulties, you may request a temporary waiver to allow submission after the problems are resolved.
VI. SUBMISSION INSTRUCTIONS FOR PHYSICAL STORAGE MEDIA

If you choose to submit electronic data files concurrently with paper reports by mail, you should mail the submission package to the address below. The package should include two copies of the electronic data files on CD-ROM. The address is:

Lot Distribution Data Coordinator (HFM-220)  
Office of Biostatistics and Epidemiology  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
Suite 200N  
1401 Rockville Pike,  
Rockville, MD 20852-1448