NDA 210136

NDA APPROVAL

Braeburn Inc.
450 Plymouth Road
Suite 400
Plymouth Meeting, PA 19462

Attention: Ruchira Kannambille
Director, Regulatory Affairs

Dear Ms. Kannambille:

Please refer to your new drug application (NDA) dated and received July 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BRIXADI (buprenorphine) extended-release injection for subcutaneous use.

We acknowledge receipt of your amendment dated November 23, 2022, which constituted a complete response to our December 15, 2021, action letter.

This NDA provides for the use of BRIXADI for the treatment of moderate to severe opioid use disorder (OUD) in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, submitted on June 1, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 210136**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for BRIXADI (buprenorphine) extended-release injection shall be 36 months from the date of manufacture when stored at controlled room temperature, 25°C, with excursions permitted from 15°C to 30°C.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The prevalence of OUD in the pre-adolescent and adolescent (under age 17) population is very low, and this product

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

would not be suitable for treating iatrogenic opioid dependence (i.e., physical dependence without meeting criteria for OUD).

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to: identify unexpected serious risks that may occur if elemental impurities leach from the container closure system; nor to identify unexpected serious risks that may occur from other compounds, both identified and unidentified, present in your product.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4439-1 Conduct a study to quantitate the level of elemental impurities that could be leached from the container closure system over the course of the shelf-life and provide a toxicological risk assessment to justify the safety of the levels detected.

The timetable you submitted on May 17, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2023
Study Completion:	10/2024
Final Report Submission:	03/2025

Evaluate elemental impurity levels in at least three batches of drug product on stability at 12 and 24 months or provide adequate extraction data using suitable solvents (e.g., nitric acid for elementals from glass).

4439-2 Conduct a study using validated methods to confirm the identity of the unspecified (b) (4), the unidentified compound with relative retention time (RRT) of (b) (4) minutes, the unknown compound containing (b) (4) with RRT of (b) (4) minutes, and the unknown compound with (b) (4) with RRT of (b) (4) minutes that were detected in your leachable studies above the safety concern threshold of 5 mcg/day and the levels of the identified leachables (b) (4)

[redacted](b) (4) and provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

The timetable you submitted on May 17, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2023
Study Completion:	10/2025
Final Report Submission:	03/2026

Evaluate at least three batches of your to-be-marketed drug product at multiple timepoints over the course of your stability studies to identify trends in leachable levels over time. Base the final safety assessment on the maximum predicted levels of leachables identified in individual batches to determine the safe level of exposure via the label-specified route of administration. Do not combine samples from different batches. Once chemical identification is confirmed for the unknown compounds, provide a toxicological risk assessment for each of these compounds and any other compounds detected at ≥5 mcg/day.

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of precipitated withdrawal when BRIXADI is initiated at full blocking doses.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4439-3 Conduct a clinical trial to evaluate precipitated withdrawal when BRIXADI is initiated at a full blocking doses, i.e., weekly doses of 24 mg and 32 mg, and monthly doses of 64 mg and 96 mg. Prespecify case definitions of precipitated withdrawal, lack of tolerability, and dose inadequacy for the purpose of quantifying the risks of a rapid initiation of BRIXADI.

The timetable you submitted on May 17, 2023 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	07/2023
Final Protocol Submission:	01/2024
Study Completion:	01/2026
Final Report Submission:	07/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol to your IND 114082 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for BRIXADI to ensure the benefits of the drug outweigh the risk of serious harm or death that could result from intravenous self-administration.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that BRIXADI can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious harm or death that could result from intravenous self-administration listed in the labeling of the drug.

Your REMS includes the following element to mitigate this risk:

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the element to assure safe use (outlined above) that requires pharmacies, practitioners, or health care settings that dispense the drug be specially certified.

Your proposed REMS, submitted on November 23, 2022, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce BRIXADI into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

REMS Implementation and Operations

1) Program Implementation (for the 6-month REMS assessment only)
    a. Date of first commercial distribution of BRIXADI
    b. Date that the REMS website went live
    c. Date when healthcare settings or pharmacies could become certified by fax, mail, email, and online
    d. Date first healthcare setting or pharmacy became certified
    e. Date when the REMS Call Center is fully operational

2) REMS Certification

a. Healthcare Settings

i. Total number of certified healthcare settings

ii. Number and percentage of newly certified healthcare settings, stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility, institution, opioid treatment program, Department of Defense (DoD) facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by United States (US) Census)

iii. Number and percentage of certified healthcare settings that have received at least one BRIXADI shipment during the reporting period, stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility, institution, opioid treatment program, DoD facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by US Census)

iv. Number and percentage of certified healthcare settings that have dispensed BRIXADI at least once during the reporting period, stratified by healthcare setting type (i.e., group practice, hospital, independent practice, Veterans Administration facility, institution, opioid treatment program, DoD facility, closed healthcare system, outpatient clinic, or other) and geographic region (as defined by US Census)

b. Pharmacies

i. Total number of certified pharmacies

ii. Number and percentage of newly certified pharmacies, stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by US Census)

iii. Number and percentage of certified pharmacies that have received at least one BRIXADI shipment during the reporting period, stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by US Census)

iv. Number and percentage of certified pharmacies that have dispensed BRIXADI at least once during the reporting period, stratified by pharmacy type (i.e., specialty, retail, or other) and geographic region (as defined by US Census)

c. Wholesaler/Distributors

i. Total number of authorized wholesalers/distributors

ii. Number and percentage of newly authorized wholesalers/distributors

iii. Number and percentage of active wholesalers/distributors (i.e., have shipped BRIXADI at least once during the reporting period)

3) REMS Utilization

a. Number of BRIXADI shipments from wholesalers/distributors, stratified by shipment location (i.e., healthcare setting, pharmacy, or other location)

b. Number of BRIXADI dispenses (first-fills and refills), stratified by dispensing entity (i.e., healthcare setting or pharmacy)

c. Number of unique patients prescribed BRIXADI, stratified by dispensing entity (i.e., healthcare setting or pharmacy)

d. Number of BRIXADI injections administered at a pharmacy, stratified by pharmacy type (i.e., specialty, retail, other)

4) REMS Infrastructure and Performance

a. BRIXADI REMS Call Center Report

i. Number of contacts by stakeholder type

ii. Summary of reason for calls (e.g., “enrollment question, location of certified healthcare setting, etc.”) by reporter (i.e., prescriber, authorized representative, healthcare setting, pharmacy, patient/caregiver, other), accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (whichever accounts for the greater number of calls)

iii. The number of REMS issues/complaints reported to the REMS Call Center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (whichever accounts for the greater number of calls) and the resolution (if applicable)

iv. A summary and analysis of calls that may indicate an issue with patient access or burden on the healthcare delivery system. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues.

v. A summary report of corrective actions resulting from issues identified

vi. The number of REMS materials requested through the REMS Call Center

b. REMS Website

i. Number of visits and unique visits to the BRIXADI REMS website

ii. The number of REMS materials downloaded or printed for each material

5) REMS Compliance

a. Provide a report of audit findings for each stakeholder (i.e., certified healthcare settings, pharmacies, distributors, REMS Call Center or other entities) including but not limited to:

i. A copy of the audit plan for each stakeholder (including any auditing surveys or protocols used)

ii. The number of audits expected and the number of audits conducted. Include reasons why expected audits were not conducted and plans to audit these entities.

iii. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for group of audited stakeholders

iv. Summary report of deviations found, associated corrective and preventive action (CAPA) plans resulting from audit findings for each non-compliant entity, and the status of CAPA plans

v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken

vi. Use a unique identifier (ID) for stakeholders that had deviations to track deviations by stakeholders over time

vii. Confirm documentation of completion of training for relevant staff

viii. Verify the existence of documented processes and procedures for complying with the REMS

ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. Provide a summary of the non-compliance identified, including but not limited to:

i. A copy of the Non-Compliance Plan which addresses the criteria for noncompliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS

ii. The number of instances of non-compliance, accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:

1. The unique ID(s) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
2. The source of the non-compliance data
3. The results of the root cause analysis
4. What action(s) were taken in response and whether any follow-up is planned

iii. Number of healthcare settings and pharmacies decertified, reasons for decertification, and actions to address non-compliance

iv. Number of wholesalers/distributers deauthorized, reasons for deauthorization, and actions to address non-compliance

v. Number of shipments of BRIXADI to non-certified healthcare settings or pharmacies, or other locations (e.g., patient's home), source of report, and corrective actions to prevent shipment to non-certified settings and pharmacies, or other locations

1. Disposition of BRIXADI shipped to non-certified healthcare settings or pharmacies, or other locations (e.g., drug returned, drug administered, drug lost/stolen)
2. If the established threshold for metric 5.b.v. is not met, a root cause analysis of why the threshold was not met, and a proposed plan for specific measures or modifications to the REMS to meet the established threshold

vi. Number of BRIXADI dispenses directly to patients stratified by dispensing entity (i.e., healthcare setting or pharmacy)

1. Disposition of BRIXADI dispenses directly to patients
2. If the established threshold for metric 5.b.vi. is not met, a root cause analysis of why the threshold was not met, and a proposed plan for specific measures or modifications to the REMS to meet the established threshold

vii. Annual verification that the pharmacy's designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of healthcare setting and pharmacy recertification.

Health Outcomes and/or Surrogates of Health Outcomes

6) Safety Surveillance

   For each analysis, provide an overall summary, including a root cause analysis, and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication. The safety surveillance sources should include, but not be limited to: adverse event reports, literature searches, and internet surveillance.

   a. Provide analyses of all cases of:

      i. Known or suspected IV administration of BRIXADI, regardless of outcome, and root cause analyses of what REMS processes were not followed and allowed for IV administration

      ii. Serious adverse events related to thromboembolic disorders reported with BRIXADI

      iii. Known or suspected abuse, misuse, and overdose of BRIXADI, regardless of outcome

   b. Provide an analysis of adverse events resulting in an outcome of death

Program Outreach and Communication

7) REMS Outreach and Communication

   a. Number, dates, and means of delivery for the letters sent (and packets, as appropriate)

      i. The number and percentage of emails successfully delivered, opened, and unopened

      ii. The number and percentage of mailings successfully delivered and those returned as undeliverable

   b. Names of professional societies receiving REMS letters or other materials

   c. Source of the list of prescribers, pharmacists, professional societies, pharmacies, distributors, hospitals, closed health systems, outpatient clinics, long-term care facilities, DoD facilities, prisons, inpatient psychiatric units, and Opioid Treatment Programs

Overall Assessment of REMS Effectiveness

8) The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the

strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 210136 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether

the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 210136 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 210136/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 210136/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 210136/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 210136/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 210136

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the

final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Rita Joshi, PharmD, Regulatory Project Manager, at rita.joshi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Celia Winchell, MD
Associate Director for Therapeutic Review,
Addiction Medicine
Division of Anesthesiology, Addiction Medicine,
and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling
- REMS

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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/s/

CELIA J WINCHELL
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