NDA 018680/S-074

**COMPLETE RESPONSE**

CooperSurgical, Inc.
Attention: Regina Shih
Vice President, Global Regulatory and Clinical Affairs
75 Corporate Drive
Trumbull, CT 06611

Dear Regina Shih:

Please refer to your supplemental new drug application (sNDA) dated and received February 28, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paragard (intrauterine copper contraceptive).

We also acknowledge receipt of your amendment dated November 20, 2023, which was not reviewed for this action.

This “Prior Approval” efficacy supplement to your application provides for a new inserter intended to facilitate the single-hand placement of Paragard.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reason for this action below and our recommendation to address this deficiency.

**Deficiency Identified:**

**FACILITY INSPECTIONS**

During our recent inspection of the CooperSurgical, Inc, (FEI, 1316626, NY, USA) manufacturing facility, our field investigator could not complete the inspection because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved. Notify us in writing when this facility is ready for inspection.

**ADDITIONAL INFORMATION AND COMMENTS**

**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the

Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

Regarding your submission dated November 20, 2023, containing draft labeling for Paragard, we recommend you include that version as draft labeling in your resubmission.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

## CARTON AND CONTAINER LABELING

We have the following Carton Labeling and Placement Guide recommendations that are not approvability issues:

1. The placeholder for the lot number is missing. Add the placeholder for the lot number in accordance with 21 CFR 201.10(i)(1).
2. The placeholder for the expiration date is missing from the carton labeling. Also, as currently presented on the Placement Guide, the format for the expiration date is not defined. Add the placeholder for the expiration date in accordance with USP General Chapter <7>. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash separate the portions of the expiration date.
3. The product identifier is missing. We recommend you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

4. The NDC number lacks prominence due to the small font size. Consider increasing the font size of the NDC number.
5. We note that the "Master Carton" contains additional language that is not present on the carton (i.e., (b) (4)). We recommend removing (b) (4). Additionally, clarify the purpose of this master carton.
6. The proposed inserter has some unique task differences compared with other similar IUS products. Add "Read the Preparation Instructions and Insertion Procedure before initiating Paragard insertion because different inserters perform differently."
7. Inconsistent terminology is used on the carton to describe the Prescribing Information and Patient Information labeling. For example, the carton states: "(b) (4) NOTE: (b) (4) is provided with each unit. Please ensure (b) (4) is provided to (b) (4) (b) (4) with each patient before insertion." We recommend revising the bolded terms to be consistent with the titles of the specific labeling to which it is referring. Specifically, replace (b) (4) with the title of the specific document you are referring to (i.e., Patient Information). Additionally, we note there is no proposed (b) (4) document. We believe this is referring to the instructions contained within Section 2 of the PI, so we recommend replacing (b) (4) with "See detailed instructions in the Prescribing Information".

Placement Guide:

8. As proposed, the far-left panel and the far-right panel on your Placement Guide also serve as your container label, creating visual clutter surrounding the insertion procedure instructions. Furthermore, some required container label information is missing. For example (not all inclusive), the placeholder for the lot number and linear barcode are missing. We recommend you develop a separate container label that contains the required information separate from the insertion procedures. For example, develop a container label sticker affixed to the outside of the sterile packaging. To assist in developing your container label refer to the *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. Then, revise the left and right panel of the Placement Guide to remove any redundant unnecessary information for the purposes of decreasing label clutter on the Placement Guide.
9. You are proposing to provide your Placement Guide inside the sterile packaging. This approach prevents users from reviewing the Placement Guide prior to starting the procedure. Consider providing an additional copy of the Placement Guide inside the carton but outside of the sterile packaging.
10. We note that Step 1 in the Placement Guide is lacking critical information for the intended use of the product. Specifically:

- Does not mention keeping the button in place while moving the device forward into the tray.
- Does not warn users not to push the button back and forth multiple times to avoid creating slack in the threads
- Does not mention keeping the tray in a horizontal position during loading.

Consider adding statements to the Placement Guide to alert users of these critical handling points. For example, you may consider:

- Adding a statement similar to: “Keep button in position shown” in Step 1.
- Labeling the neutral line, so users are aware that it is the ready position and not for use in the deployment. We note that there appears to be a neutral line depicted in Step 1, but it is not labeled (highlighted below).

(b) (4)

- Adding a statement to Step 1 to inform user to keep the tray flat on a sterile horizontal surface.

11. We recommend prominently describing the use-related tasks that are unique to Paragard IUS and the proposed inserter. Consider including a description on the figure in Step 1 of the “neutral line” and include text to define what the line is intended to indicate (see red arrow):

(b) (4)

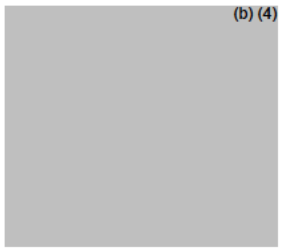
Additionally, the location of the neutral line on the figures in the Placement Guide appears to be inconsistent between steps 1, 2, and 5. Consider revisions to accurately depict the location of the neutral line in the aforementioned graphics.

Furthermore, enhance Steps 5 and 6 to show this product is deployed at the fundus.

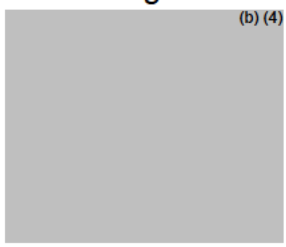
For example:

- Step 2: the neutral line in step 2 appears to be in a different location than the line in steps 1 and 5:


- Step 5: add language to image saying, “to fundus” and clarify what the line (red arrow) means in this image, it appears to be in a different location than the line in Steps 1 and 2:




- Step 6: unlike the other steps does not depict a neutral line. Consider adding the neutral line to this image:




12. The figure in Step 7 of the Placement Guide can be improved to clarify that users should trim the threads so that 3 to 4 cm protrude into the vagina. Specifically, the text “3-4 cm” is located separately from the text “Trim threads”.

    Revise the text in Step 7 to read, “Trim the threads so that 3 to 4 cm protrude into the vagina.” Additionally, revise the figure to show where the measurement starts and ends (e.g., use of lines to show the measurement and indicate where the 3-4 cm should be measured from). For example, see the red font below:


    Further, we note that the vaginal walls are depicted on the other steps (i.e., Steps 5 and 6) in the Placement Guide, but not in Step 7. To improve clarity of this step, we recommend adding the vaginal walls to the image in Step 7.

13. The language contained under Step 7 of the Placement Guide about who should insert the product can be revised for clarity. Relocate the "IMPORTANT: (b) (4) statement to the left panel of the Placement Guide or include it as part of the separate container label for the packaging.

    Replace the phrase (b) (4) with the intended meaning. For example, if phrase refers to the instructions provided in Section 2 of the PI, then revise to say, "instructions in the Prescribing Information".

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the supplemental application data.
- Include tables that compare frequencies of adverse events in the supplemental application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of reasons for subjects who had premature trial discontinuation by incorporating the dropouts from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the supplemental application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

If you have any questions, call Dorsa Jalali, Regulatory Project Manager, at 240-402-0543.

Sincerely,

*{See appended electronic signature page}*

Audrey Gassman, M.D.
Deputy Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

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AUDREY L GASSMAN
12/18/2023 11:04:00 AM