CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-906

CHEMISTRY REVIEW(S)

1. ***CHEMIST's REVIEW #2*** **First Generic*

2. **ANDA 75-906**

3. APPLICANT, Name/Address/Telephone/Fax:
American Pharmaceutical Partners (APP)
Attention: Michael Lisjak
2045 N. Cornell Avenue
Melrose Park, IL 60160
☎ 703-547-2365/*fax* 1-703-343-4269

4. LEGAL BASIS FOR ANDA SUBMISSION: *505(j)*

5. Supplement: n/a

6. PROPRIETARY NAME: none

7. Non-PROPRIETARY NAME: **Progesterone Injection** USP, 50 mg/mL

Innovator's Product Name: Steris' NDA 17-362: **Progesterone Injection, USP in Sesame Oil**

8. Supplement Provides For: n/a

9. AMENDMENTS & Other DATES:

A. **FIRM:**
06-16-00 original application
*01-24-01 minor amendment re chem, labeling & Micro issues.
*02-01-01 minor amendment re revision of test method for determ. of impurities in the DP.
04-19-01 amendment Fax withdrawal of NAMSA testing lab.
04-19-01 NC
04-20-01 fax amendment with IR spectra of DP.

B. **FDA:**
09-28-00 DBE "preliminary" Waiver request granted
08-08-00 acceptable for filing June 19, 2000.
06-18-00 e-mail from M.Bennett re first generic.
09-06-00 e-mail from H.Greenberg that Steris is RLD
07-18-00 DBE memo re waiver meets statutory requirements.
12-15-00 Micro Review #1 - not recommended.
02-22-01 Micro now acceptable
01-02-01 NA letter
02-22-01 labeling now sat.
02-21-01 Compliance Branch memo to OGD Review Support Branch

10. PHARMACOLOGICAL CATEGORY: steroid

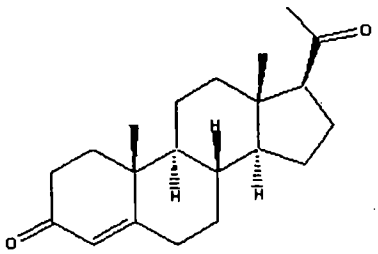
11. Rx or OTC: R_x

12. RELATED ANDA's: none

13. DOSAGE Form: injection

14. POTENCY: 50 mg/mL

15. CHEMICAL Name: Pregn-4-ene-3, 20-dione
MW 314.47



16. Records & Reports: n/a

17. COMMENTS.

A. General Comments:
This is a USP drug substance and drug product.

B. Comments & Responses from the last Action Letter:

1. We recommend that your test for color use APHA values in both the drug product release and stability specifications.
Firm's Response:
They stated that the color will be measured by using the same method in both APHA & Yellowness Index (YI-[illegible]) for the future. The spec established before of [illegible] is equivalent to NMT [illegible] in terms of APHA 10mm and will be added to both release and stability specs. See attachment I.
Our Comments:
Sat reply. The Specification Tables were corrected accordingly.

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#17B

7. In your application, page 544, is referenced the use of current USP methods for the assay determination for progesterone, but this appears not consistent with the validation report (BLD 92554)(page 602). For example, the USP method uses water/isopropanol as the mobile phase while your method reports ---. Please explain.
Firm's Response:
APP stated that they do the assay of the DS per methods described in the USP using water/isopropanol. That the validation report referenced above refers to the DMF holder's method for both assay and impurities and was referenced only to support the method used by APP.
Our Comments:
Sat. comments were provided.

18. CONCLUSIONS & RECOMMENDATIONS:
AP pending acceptable CGMP.

19. Reviewer/Branch Chief:

Robert W. Trimmer, Ph.D.	*Dave S. Gill, Ph.D.*
BRANCH IV, DIV. OF CHEMISTRY I, OGD	TEAM LEADER

Date Completed: 2-23-2001

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38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-906 APPLICANT: Am. Pharmaceutical Partners, Inc.

DRUG PRODUCT: Progesterone Injection USP, 50 mg/mL-10 mL vials

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. We recommend using APHA values for your test for color in both the drug product release and stability specifications.

2. Regarding your *drug product release specification*, please lower your limit for the "largest individual unknown" impurity, which you are currently proposing . Likewise the limit for e can be lowered from the originally proposed .

3. Regarding your *drug product stability specificatio*n, please lower your limit for the "largest individual unknown" impurity, which you are currently proposing Likewise the limit for e can be lowered from the originally proposed so, please include additional specification per USP monograph: Other requirements - It meets the requirements under Injections <1>.

4. Please correct your stability protocol to read:

   a. stability testing shall be performed initially, every 3 months during the first year, every 6 months the 2nd year, and yearly thereafter until the assigned expiry. This is applicable for both the first 3 batches and the annual check batches.

   b. Please also correct your post approval commitment (page 753) regarding stability of the finished dosage form. Storage at 23-27° should be at 60° ± 5% RH, and in both the upright and inverted orientations. At a later date, the upright orientation may be removed through the supplemental application process.

5. In addition to the tests specified in the USP, please provide adequate tests and acceptance criteria for Bacterial Endotoxins, USP <85>, and Total Microbial Count for Sesame Oil.

6. Regarding your ID test for Progesterone Injection in Table 30, the Test Method is listed as USP (which uses IR for the test). However, in Table 31 and your COA for the Exhibit batch, you report a test. Please use the USP specific test method rather than the non-specific test method. You may propose the method and another non-specific test method as an alternate.

7. In your application, page 544, you referenced the use of current USP methods for the assay determination for progesterone, but this is not consistent with the validation report (BLD 92554 on page 602). For example, the USP method uses water/isopropanol as the mobile phase while your method reports methanol/water. Please explain.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Since the subject drug product is an official article in the USP, the approval to use an analytical procedure that differs from that in the USP does not release you from any obligations to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official methods and procedures in the USP will be considered conclusive.

3. Please provide additional long-term stability data, if available.

4. Your response must also address the labeling deficiencies.

5. Your response must also address the microbiology deficiencies.

Sincerely yours,

RMPatel

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research