# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**85239**

## CHEMISTRY REVIEW(S)

| CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT | Statement Date: | NDA NUMBER: 85-239 |
|---|---|---|

NAME AND ADDRESS OF APPLICANT
Chromalloy Pharmaceuticals, Inc.
Carter-Glogau Laboratories Division
Glendale, AZ 85301

ORIGINAL
AMENDMENT xxxxx
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
manufacturing information, labeling, controls

DATE(s) of SUBMISSION(s)
4-21-78, 5-12-78, 9-12-78, 1-18-79 and 1-26-79

| PHARMACOLOGICAL CATEGORY | NAME OF DRUG | HOW DISPENSED |
|---|---|---|
| estrogen | estrone | RX xxxxx OTC _____ |
| **DOSAGE FORM(S)** | **POTENCY(IES)** | **RELATED IND/NDA/DMF** |
| suspension | 5 mg./ml. | |
| **STERILIZATION** | **SAMPLES** | |
| | | |

**LABELING**
see medical officer's review of 1-17-79

**BIOLOGIC AVAILABILITY**
currently not required

**ESTABLISHMENT INSPECTION** related HFD-322 memo for Carter-Glogau of 10-11-78 based on profile of 8-11-78 for Carter-Glogau and 7-17-78 for

**COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS**
satisfactory

**PACKAGING**
included

**STABILITY**
**Protocol:** included
**Exp. Date:** 24 mo.

**REMARKS AND CONCLUSION:** approval majarski

JSI 2/16/79

| CHEMIST's REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT | Statement Date: | NDA NUMBER: 85-239 |
|---|---|---|

NAME AND ADDRESS OF APPLICANT
Chromalloy Pharmaceuticals, Inc.
Glendale, Az 85301

ORIGINAL
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE ccxxx
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT
comment on labeling

DATE(s) of SUBMISSION(
3-27-78

| PHARMACOLOGICAL CATEGORY | NAME OF DRUG | HOW DISPENSED |
|---|---|---|
| estrogen | estrone | RX ~~xxxxx~~ OTC ____ |
| DOSAGE FORM(S) | POTENCY(IES) | RELATED IND/NDA/DMF |
| suspension-injectable | 5 mg./ml. | |
| STERILIZATION | SAMPLES | |
| | | |

LABELING
satisfactory

BIOLOGIC AVAILABILITY

ESTABLISHMENT INSPECTION

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
additional information required

PACKAGING

STABILITY
Protocol:

Exp. Date:

REMARKS AND CONCLUSION: rev w/f majarski

/S/ 1/29

CHEMIST'S REVIEW FOR
ABREVIATED NEW DRUG APPLICATION
OR SUPPLEMENT

Statement Date

85-239
AF Number

me and address of Applicant (City and State)

Chromalloy Pharmaceuticals, Inc.
Glendale AZ 85301

Original
Amendment xxxxx
Supplement
Resubmission
Correspondance
Report
Other

rpose of Amendment/Supplement

Patient Package Insert

Date(s) of Submission(s)

10-31-77

| armacological Category | Name of Drug | |
|---|---|---|
| estrogen | estrone | |
| sage Form(s) | Potency(ies) | How Dispensed |
| suspension | 5 mg./ml. | $R_x$ xxxxx<br>OTC |
| erilization | Samples | Related IND/NDA/DMF |

beling per medical officer's review of 12-1-77 PPI is satisfactory - However, in keeping with comments to firm in other applications, firm is notified that approval for a PPI comment to all manufactured estrogen products, approval is necessary for all the listed products.

ɔlogic Availability

tablishment Inspection
requested

nponents, Composition, Manufacturing and Controls

per issuing letter of 11-9-77

:kaging

per issuing letter of 11-9-77

ıbility
rotocol

per issuing letter of 11-9-77

Expiration Date

s and Conclusion

rev w/f majarski

/S/ 4/78

EVIEWER DATE

BREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

85-239

AF Number

me and address of Applicant (City and State)

**Chromalloy Pharmaceuticals, Inc.**
**Carter-Glogau Laboratories Division**
**Glendale, AZ 85301**

Original
Amendment **xxxxx**
Supplement
Resubmission
Correspondance
Report
Other

rpose of Amendment/Supplement

**manufacturing, labeling**

Date(s) of Submission(s)

**6-28-77**

| irmacological Category | Name of Drug | |
|---|---|---|
| **estrogen** | **estrone** | |
| sage Form(s) | Potency(ies) | How Dispensed |
| **suspension** | 5mg./ml. | $R_x$ **xxxxx** OTC |
| erilization | Samples | Related IND/NDA/DMF |
| **dditional information** | | **85-239** |

**see medical officer's review of** 7-21-77

Logic Availability

**not required**

ablishment Inspection

**requested 11-4-77**

ponents, Composition, Manufacturing and Controls

**per issuing letter**

kaging **additional information**

bility **per issuing letter**
rotocol

xpiration Date **5 years requested; 2 years recommended**

ks and Conclusion

**rev'r w/f majarski**

/S/ 11/7/77

VIEWER DATE

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

Statement Date

NDA Number
85-239

AF Number

Name and Address of Applicant (City and State)

Carter-Glogau Laboratories Division
Chromalloy Pharmaceuticals, Inc.
Glendale, AZ 85301

Original XXXXX
Amendment
Supplement
Resubmission
Correspondance
Report
Other

Purpose of Amendment/Supplement

Date(s) of Submission(s)
12-9-76

| Pharmacological Category | Name of Drug | |
|---|---|---|
| estrogen | estrone | |
| Dosage Form(s) | Potency(ies) | How Dispensed |
| sterile suspension | [redacted] 5 mg./ml. | Rx XXXXXX<br>OTC |
| Packaging/Sterilization | Samples | Related IND/NDA/MF |
| requested | | |

Labeling

see medical officer's review

Biologic Availability

not required

Establishment Inspection

requested 4-12-77

Components, Composition, Manufacturing and Controls

as per issuing letter
see attached

Remarks

rev w/f majarski

Conclusion

/S/ 4/15/77

REVIEWER

DATE

Basis for suspension formulae and other characteristics:

1. The Theory and Practice of Industrial Pharmacy: Second Edition 1976. Chapters 4 and 5 Theories of Dispersion Techniques; Pharmaceutical Suspensions.

2. Nash,R.A.: Drug & Cosmetic Ind., 97: 843, 1965; 98: 39, 1966.

Basis for Manufacturing information:

1. As above

2. See attached for questions FDA is asking its inspectors to check for in sterility compliance program.

lated suspensions frequently result in pharmaceutically poor suspensions. Flocculated suspensions are to be preferred because they have less tendency to cake on standing and are therefore more readily redispersible. Obviously, a pharmaceutical suspension must be redispersible on only mild agitation to ensure dosage uniformity.

The tendency of particles to flocculate depends on the forces of attraction and repulsion between them. If the repulsion is of sufficient strength, the particles remain dispersed; if not they coagulate. The attractive forces between particles is thought to be due to London or van der Waals forces. The van der Waals forces of intermolecular attraction were named after this scientist who used certain constants in the gas equation he formulated as a correction to the ideal gas law. The forces are due to combinations of ionic, dipole, and induced dipole interatomic and intermolecular phenomena effected through dipole moments; the London forces terminology emphasizes the induced dipole aspects. For example, in a suspension of clay particles, as an increasing amount of sodium chloride is added, the repulsive forces decrease. As increasing amounts continue to be added, the repulsive forces can no longer counteract the van der Waals attraction, and the system flocculates.

Sedimentation and flocculation rates are properties of suspension systems governed by particle size, particle-particle interactions, densities of the particles and the medium, and the viscosity of the continuous phase. Subsidence is a term often used to describe the settling of a flocculated system and refers to the settling rate or descending of the boundary between the sediment and the clear supernatant above it. In deflocculated polydispersed systems (i.e., those having many different particle sizes present) this measurement is of little value because the boundary is not well defined. In this case the large particles settle downward more rapidly than the smaller particles, whereas in concentrated deflocculated suspensions the larger particles exhibit hindered settling, and the smallest settle more rapidly. In flocculated suspensions, the particles are linked together into flocs which initially settle according to the size of the floc and porosity of the aggregated mass. Later the rate is governed by compaction and rearrangement processes. A clear supernatant is formed on settling, since even the smallest particles are entrapped in the mesh-like network of the floc. Intermediate states are possible where all particles are not associated with flocs.

As experimental examples, it is noted that Jones, Matthews, and Rhodes studied the stability of sulfaguanidine suspensions as they were affected by electrolyte (aluminum chloride), type and concentration of surfactant (cetyltrimethylammonium bromide, polysorbate 80), and nature of vehicle (water with various amounts of glycerol).[5] They achieved optimum stability by balancing the adjuvants to obtain a controlled flocculation. Also of interest, Carless and Ocran related, in hectorite dispersions for example, particle shape, particle interaction mediated by added electrolytes, and some rheological properties.[6] As reported in a recent patent, Storz,[7] doing research on intramuscular injectables containing steroidal and other water-insoluble medicaments, found that a pharmaceutically elegant, readily redispersible, stable, well-preserved, moderately flocculated suspension would form in an aqueous vehicle having as additives a non-ionic polyether surfactant (up to 1% of, e.g., polysorbate 80, PEG's, polyoxyethylenepolyoxypropylene block polymers) and normal preservative concentrations of benzyl alcohol (0.5–1.5%) and the parabens (0.1–0.3%).

To determine whether a suspension is flocculated, a differential manometer can be used to compare the pressure of a suspension near its bottom and top in a container. This device has been described by Tingstad.[8] A flocculated suspension shows the same pressure at both points as it exerts little or no pressure on the liquid because the particles essentially support each other. A nonflocculated suspension, however, exerts more pressure near its bottom.

## Sedimentation Rates

With regard to actual settling rates, the well-known Stokes relation describes the

It will be informative to examine some additional low and high solid content formulas and observe their characteristics. The following table shows the components that are required to prepare a model parenteral suspension; this route of administration limits the formulator to a rather narrow range of additives.

The samples are best prepared by making a concentrate of the dispersant in a volume equal to 10% of the final volume, thoroughly mixing in the active ingredient with the help of a colloid mill or other device, and adding the remaining components to a solution of the preservative(s). The latter should be prepared using about 80% of the final total volume. This solution is then added to the portion containing the active ingredient, and sufficient purified water is added to bring it to the final volume.

TABLE 5-1. *Low Solids Content Suspensions*

| Sample | Concentration in mg./ml. | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *A* | *B* | *C* | *D* | *E* | *F* | *G* | *H* |
| Steroid* | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Polysorbate 80† (dispersant) | 0.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Sodium citrate (buffer) | — | — | — | 10.0 | — | — | — | — |
| Sodium chloride (for isotonicity) | 0.0 | 9.0 | 9.0 | — | 9.0 | 9.0 | 9.0 | 9.0 |
| Benzyl alcohol (preservative) | — | — | 9.0 | 9.0 | 9.0 | — | 9.0 | — |
| Chlorobutanol (preservative) | — | — | — | — | 5.0 | 5.0 | — | — |
| Methylparaben (preservative) | — | — | — | — | — | — | 1.8 | 1.8 |
| Propyl paraben (preservative) | — | — | — | — | — | — | 0.2 | 0.2 |
| Purified Water q.s. to 1.00 ml. | | | | | | | | |

*Cortisone acetate, prednisolone acetate, etc.

†Span 40 or Tween 40 could also be used. As noted previously, these are trademarks of ICI United States Inc.

The observations are

A—no dispersion or very little wetting of solid; this may depend on the recrystalization solvent (acetone versus dimethylformamide).

B—good dispersion, rapid settling, caking.

C—good dispersion, rapid settling, severe caking, poorly redispersible, deflocculated.

D—good dispersion, rapid settling, easily redispersible, slightly flocculated.

E—good dispersion, slow settling, moderately flocculated.

F—good dispersion, slow settling, finely flocculated.

G—good dispersion, slow settling, flocculated.

H—good dispersion, slow settling, coarsely flocculated.

It is important to note that protective colloids, such as polyethylene glycol 4000, sodium carboxymethycellulose 7LP or 7MP, and methylcellulose all modify these characteristics. Sorbitol or dextrose can be included to adjust density.

Inspectors are instructed in the new program to describe "in detail" any practices in product sterilization processing which may:

- *Add* or *remove* biological contaminants to or from the device
- Add to presterilization microbial levels
- Adversely effect immediate package integrity which may compromise sterility
- Relate to handling or sanitizing systems which physically contact the device (conveyors, U-V lights, etc.)
- Indicate a possible compromise of sterility or represent a potential for contamination in the opinion of the investigator.

Besides being more specific in nature than the previous sterility compliance program, the new document includes sterility evaluations for biological indicators and radiation sterilization processes. As in the original program, imported devices are not covered.

## QUESTIONS FDA IS ASKING ITS INSPECTORS TO CHECK FOR IN STERILITY COMPLIANCE PROGRAM

*List reproduced by "The Gray Sheet" from the Appendix to FDA's compliance program. FDA's instructions advise inspectors to take the list with them and fill in answers to each parameter.*

### 1 GENERAL INFORMATION

Firm and/or location that sterilizes device (if different)
Production rate (units/month)
Ave. particulates (no./unit)
oxic residues (mg/gram, list)
Type of packaging & material used
Shelf life (expiration date)
Average presterilization microbial count (No./unit)

### 2 STERILIZATION-GENERAL

Type of sterilization
Validation of cycle (D value)
Determined at (site)
Determined by (firm? consulting lab?)
Sterility confidence (%) or probability of non-sterile unit

### 3 STEAM STERILIZATION

Steam manufacturer
Sterilization cycle
Time (min.)
Temperature (°C)
Pressure (mg Hg)
Pressure comedown rate (mg Hg/min)
Saturated steam (%)
Parameter monitoring (yes/no) *[See footnote]*

### 4 RADIATION STERILIZATION

Sterilization mfr.
Radiation source supplier
Radiation source (e.g. cobalt 60)
Radiation type ( $\alpha \beta \gamma$ )
Dosimeter type
Dose rate (Mrad/hr)
Uniformity of dose rate (±%)
Total dose (Mrad)
Temperature
Parameter monitoring (yes/no) *[See footnote]*

### 5 GAS STERILIZATION

Sterilizer mfr.
External humidification
Time (hr.)
Relative humidity (%)
Temperature (°C)
Sterilization cycle vacuum (mm Hg absolute)
Air venting (yes/no)
Prehumidification dwell (hr.)
Temperature (°C)
Relative humidity (%)
Sterilant concentration in chamber (mg/liter)
Sterilant/carrier used (%)
Exposure to sterilant (hr.)
Pressure comedown rate (mm Hg/min.)
Sterilant exhaust (hr.)
Parameter monitoring (yes/no) *[See footnote]*

### 6 BIOLOGICAL INDICATORS

Qualifications of responsible person (e.g., BS, experience, special training)
Adventitious indicator (inoculated carrier) – Inoculated product
Organism used; type (genus, species, brand name if commercial) & population (no./carrier)
Assay procedure (e.g., USP)
Optimal growth medium
No. of carriers tested
Quarantine period (days)
Elapsed time (hr.) between removing carriers from sterilizer & testing
No. of lots resterilized because of positive biological indicators
Does indicator meet USP XIX performance levels for steam or ETO biological indicators

### 7 PRODUCT STERILITY TESTING

Qualifications of responsible person (e.g. BS)
Assay procedure (e.g. USP)
Whole unit tested
Unit tested by fluid rinse?
No. of units tested
Percentage of lot tested
Elapsed time (hr.) between removal from sterilizer & testing
Quarantine period (days)
No. of lots resterilized because of positive sterility tests

Footnote: *If yes, which parameters and by what means (e.g. temperature by recording thermometer)*