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14. ABSTRACT During the period October 22, 2010 to October 21, 2011, the project personnel continued to perform chemical/physical analyses on bulk pharmaceutical substances and formulated drug products, and to develop dosage formulations of interest to the USAMRMC Drug Development Program for parasitic and infectious diseases, chemical and biological defense, etc. Specific objectives were to design, develop, validate, and apply methods to determine chemical and physical characteristics of the bulk drugs, drug products, to determine their stability under defined conditions, to prepare formulations of bulk drugs for biological testing, and to coordinate ongoing stability studies on an artesunate dosage form with a subcontractor.					
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INTRODUCTION

This annual report for Contract W81XWH-09-C-0022 covers the period from October 22, 2010 — October 21, 2011. The report consists of an overview of the major activities, a listing of the specific tasks performed, reports submitted, and descriptions of special projects performed. The report also includes a listing of personnel receiving pay from this effort, a bibliography of all publications, and meeting abstracts that resulted from this contract during the report period.

This contract is concerned with analytical, characterization, and stability studies of chemicals, drugs, and drug formulations, and with development and manufacture of dosage formulations. The studies are monitored by Mr. William Y. Ellis, the Contracting Officer Representative (COR), Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR).

The overall objective of this project is the operation of an analytical laboratory to determine the identity, purity, strength, quality, physical and chemical properties, and stability of bulk pharmaceutical substances and formulated drug products, and to develop and manufacture, in limited quantities, dosage formulations of interest of the USAMRMC Drug Development Program for parasitic and infectious diseases, chemical and biological defense, anti-viral studies, etc. Specific objectives are to design, develop, validate, and execute methods to determine the following characteristics of candidate bulk pharmaceutical substances and formulated drugs, and to develop and manufacture, in limited quantities, dosage formulations.

- Identity, purity, and strength;
- Stability;
- Other physical and chemical characteristics, including weight variation, content uniformity, and other such compendial requirements;
- Qualitative and quantitative determination of impurities;
- Develop and manufacture, in limited quantities, dosage formulations; and
- Special projects not covered by the above headings.



ANNUAL REPORT (2010-2011)

OVERVIEW

During the contract period October 22, 2010 to October 21, 2011, our project work continues to focus on stability determination of the SRI- and the Dalton-manufactured artesunic acid (AS) IV drug products to ensure their suitability for ongoing clinical trials. Stability results from SRI Batch # 14462-16 indicate stability for at least 48 months at +5°C and at least 51 months at -20°C, thereby, enabling its ongoing clinical trials to continue.

Stability results from AS Dalton Lot 241-1-10-01 indicate stability for at least 18 months at +5°C and at 25°C. Results from Dalton units stressed at 30°C for 12 months and at 40°C for 9 months also indicate stability, although trace signs of decomposition are beginning to appear. Results from Dalton units stressed at 40°C for 12 months indicate definite decomposition. Stability studies at +5°C and at 25°C are continuing but those at 30°C and 40°C are completed.

Also, samples of bulk AS are determined stable for at least 78 months under our laboratory shelf-life conditions.

Solution stability of paromomycin and gentamicin solutions at several pH's and temperatures was a major study; preparations of topical creams of several active pharmaceutical ingredients were completed.

Topical cream preparations of anti-leishmaniasis agents have been prepared and submitted for testing. Preparations intended for drug prolongation *in vivo* resident time have been prepared and submitted for testing.

The identification and assay of bulk drug substances and dosage formulations continued throughout the contract period.

SPECIFIC TASKS PERFORMED AND REPORTS SUBMITTED

During the contract period October 22, 2010 to October 21, 2011, the following tasks were performed and the reports submitted to the COR.

1. WR002975;BJ08214, Lot AP-X-45, characterization of bulk primaquine phosphate, Report No. 1250.
2. WR002975;BJ08214, Lot AP-X-45, preparation of a 1% primaquine phosphate formulation in O-acetyl-tributylcitrate, Report No. 1270.
3. WR002975;BJ08214, Lot AP-X-45, preparation of a 1% primaquine freebase formulation in O-acetyl-tributylcitrate, Report No. 1270.
4. WR006058;BU24754, preparation of 15% disulfiram topical creams in Eucerin and in TEVA paromomycin/gentamicin placebo, Report No. 1265.
5. WR006058;BU24754, development of an assay for disulfiram in its topical cream formulations, Report No. 1266.
6. WR006058;BU24754, preparation of 10% disulfiram topical creams in Eucerin and in TEVA paromomycin/gentamicin placebo, Report No. 1272.
7. WR035928;BP21669, characterization of Lot No. 9050ES48E bulk paromomycin sulfate, Report No. 1252 and revised Report No. 1252.
8. WR035928;BP21669, investigation on aqueous stability of 15% paromomycin (freebase) solutions stored 30 days at 5°, 25°, 40°, and at 60°C, SRI Report No. 1261.
9. WR035928;BP21669, pH profile determination on a 15% solution of paromomycin sulfate by alkali titration, SRI Report No. 1264.
10. WR035928;BP21669, investigation on stability of 0.5% paromomycin (freebase) in pH 4, 5, 6, 7, and 8 solutions stored 30 days at 25°, 40°, and 60°C, SRI Report No. 1268.
11. WR035928;BP21669/WR073633;BM18591R, investigation on stability of 0.5% paromomycin (freebase)/0.5% gentamicin (freebase) in pH 4, 5, 6, 7, and 8 solutions stored 30 days at 25°, 40°, and 60°C, SRI Report No. 1269.
12. WR073633;BM18591, Lot No. 3-GMF-N-6014, characterization of bulk gentamicin sulfate, SRI Report No. 1253.

13. WR073633;BM18591R, investigation on stability of 0.5% gentamicin (freebase) in pH 4, 5, 6, 7, and 8 solutions stored 30 days at 25°, 40°, and 60°C, SRI Report No. 1267.
14. WR073633;BM18591R, investigation on aqueous stability of 0.6% gentamicin (freebase) solutions stored 30 days at 5°, 25°, 40°, and at 60°C, SRI Report No. 1261.
15. WR228275AD;BN42563, preparation of topical creams of a quinazoline analogue in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1275.
16. WR229870;BU29857, characterization of stiboglucanato de sodio solution, SRI Report No. 1254.
17. WR229870;BU29866, characterization of stiboglucanato de sodio solution, SRI Report No. 1251.
18. WR232155AB;BN46661, preparation of topical creams of a second quinazoline analogue in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1275.
19. WR256283;BR29487, chemical and sterility/endotoxins stability of artesunic acid clinical dosage form, SRI Batch No. 14462 stored 48 months at 5°C, SRI Report No. 1256.
20. WR256283;BR29487, chemical and sterility/endotoxins stability of artesunic acid clinical dosage form, SRI Batch No. 14462 stored 51 months at -20°C, SRI Report No. 1257.
21. WR256283;BQ36281, BQ37377, and BQ38641, 78-months shelf-life chemical stability of bulk artesunic acid, SRI Report No. 1263.
22. WR256283;BQ37377, 78-months shelf-life chemical stability of an ethylene oxide-treated bulk artesunic acid, SRI Report No. 1262.
23. WR621305, characterization of a sample of 17- α -ethynylestradiol-3-sulfate, sodium, SRI Report No. 1260.
24. WR261361;BU30556, characterization of a sample of 17- α -ethynylestradiol-3,17-disulfate, disodium, SRI Report No. 1259.
25. WR279377;BN69575R, characterization of Lot N4272, 250-mg azithromycin tablets, SRI Report No. 1258.

26. WR282644;BP12106, investigations on solubility of artelinic acid in alkaline pH phosphates solutions, SRI Report No. 1276.
27. WR282644;BP12106, review of comparative artelinic acid solubility in phosphate and carbonate solutions, SRI Report No. 1277.
28. WR299948(WR073633);BS89826, pH profile determination on a 0.5% and a 15% solution of paromomycin sulfate by alkali titration, SRI Report No. 1264.
29. WR299958, characterization of a gift sample of decoquinat, SRI Report No. 1255.
30. WR319713;BU57560, topical cream preparations of this dinitroanilino-derivative in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1273.
31. WR319769;BU57557, topical cream preparations of a second dinitroanilino-derivative in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1273.
32. WR621183;BU27540, topical cream preparations of pseudomycin A in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1274.
33. WR621184;BU27559, topical cream preparations of pseudomycin B in Eucerin and in TEVA paromomycin/gentamicin placebo, SRI Report No. 1274.
34. Preparation of A. Salatinjants drug solutions #1, #2, and #3, SRI Report No. 1271.

SPECIAL PROJECTS

Among the special projects carried out during this report period, topical cream preparation of anti-leishmaniasis agents was the most important. The stimulus for this work stemmed from the development of topical creams of paromomycin and gentamicin conducted by investigators at the University of Iowa and later by scientists at TEVA. Compared to the science that went into the investigations performed at those institutions, our contributions were rudimentary. Nevertheless, we were able to produce physically homogeneous, stable topical cream formulations of several potentially active anti-leishmaniasis agents. The topical cream formulations prepared and submitted for biological testing are cited in Task Performed item numbers 4, 5, 6, 15, 18, 30, 31, 32, and 33.

There continues to be need for increasing drug plasma time to obtain enhancement of drug efficacy. A number of methods have been reported to meet this need. These methods, in general, involve preparation of slow-release formulations of the drug, which usually are treated as different drug entities. In 1987, a US patent was issued to Aida Salatinjants. The patent claims that when quinine dihydrochloride is administered as solutions in combination with the drugs (vehicles) claimed in this patent, the plasma time of quinine is significantly enhanced. We prepared and closely studied these patented drugs (vehicles), but found them difficult to use and understand. The main difficulty with these drugs (vehicles) prepared following the patent procedures was that they are mixtures and not solutions. As such, they could not serve as vehicles (solvents) of administration in the usual sense. Moreover, two of the three prepared claimed drugs (vehicles) readily developed mold growth. Nevertheless, samples of these patent-claimed drugs (vehicles of mixtures) were prepared and submitted for evaluation. Drugs prepared according to the patent procedures are cited in Task Performed item number 34. Also prepared for prolongation of *in vivo* resident time were primaquine solutions in O-acetyl-tributyl citrate, cited in Task Performed item numbers 2 and 3.

PUBLICATIONS AND PRESENTATION

No publications or presentations resulted from investigations conducted during the report period.

AWARDS

No awards were received during the report period.

PERSONNEL

A listing of personnel who received major contract support during the report period is as follows:

Peter Lim, P.I.
Ronald Spanggord, Assistant P.I.
Patrick Macauley, Chemist
Jennifer Wang, Chemist

SUMMARY/CONCLUSIONS

Results from a continuing stability study on SRI-manufactured Batch# 14462 artesunate IV dosage form units stored at 5°C have shown stability for at least 48 months and those stored at -20°C have shown stability for at least 51 months. These results enabled the clinical use of this batch to continue.

Results from a continuing stability study conducted at Dalton on the Dalton-manufactured Lot 241-1-10-01 artesunate IV dosage form units stored at 5°C and at 25°C are stable for at least 18 months. Units stressed 9 months at 30°C and 40°C are beginning to show traces of decomposition. Units stored 12 months at 40°C showed definite decomposition. Studies at 30°C and 40°C are completed; those at 5°C and at 25°C are continuing. Results from the 5°C and at 25°C studies enable the clinical use of the Dalton-manufactured lot to continue.

Results from stability studies on paromomycin in solutions at pH 4, 5, 6, 7, and 8, stored at 25°, 40°, and 60°C over 30 days indicate all solutions at 25° are stable for at least 30 days. At 40°, stability is maintained at pH 4-6 for at least 30 days; at pH 7 and 8, however, ~10% decomposition has occurred after 33 days. At 60°, all solutions showed decomposition throughout the study, with those at pH 4 showing the least and those at pH 8 the most, ~30% after 30 days.

Results from comparable stability studies on gentamicin indicate stability in all solutions over the entire study period.

Results from comparable stability studies on paromomycin/gentamicin mixtures are identical to those found for the respective, individual antibiotic.

Results from shelf-life stability study on bulk artesunate indicate stability for at least 78 months, when stored under our laboratory conditions.

Nine topical cream preparations of anti-leishmaniasis agents have been prepared and submitted for testing.

Five preparations intended for drug prolongation *in vivo* resident time have been prepared and submitted for testing.

The project team continues to provide solutions to the Army's analytical chemical problems.



Respectfully Submitted:

A handwritten signature in black ink, appearing to read 'Peter Lim', written over a horizontal line.

Peter Lim, Principal Investigator

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