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Chemicals, Bulk Drugs and Drug Formulations

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13. ABSTRACT (Maximum 200 words)

The overall purpose of this contract was to perform chemical/physical analyses on bulk pharmaceutical substances and formulated drug products 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 on bulk drug and drug products.

For the entire contract period, 1 August 1991 to 30 June 1997, 125 samples of bulk drugs and dosage formulations were analyzed for identity, purity or potency; 133 samples were studied for stability and solubility. Four chiral separation methods were developed and validated, and 11 other chemical assay methods were validated. Special projects included the development and application of assays for determining protein content, residual solvents, and other relevant components in microsphere vaccine preparations. A second special project was the development and application of an assay for determining bis(chloromethyl) ether in HI-6 bulk drugs. Posters were presented in the 1993 and 1996 Medical Defense Bioscience Reviews. One publication appeared in press and a second has been accepted for publication.

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FOREWORD

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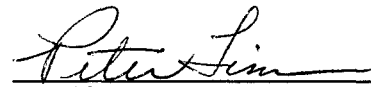
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✓ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

_____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

_____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

_____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.


PI - Signature

Oct. 1997

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INTRODUCTION

This final report for Contract DAMD17-91-C-1135 covers the period from 1 August 1991 to 30 June 1997. The report consists of a listing of the compounds/samples analyzed and a summary of the number of the types of studies performed. The report also includes a listing of personnel receiving pay from this effort and a bibliography of all publications and meeting abstracts that resulted from this contract.

This contract was concerned with the analytical, characterization, and stability studies of chemicals, drugs, and drug formulations. The work was monitored by Mr. William Y. Ellis, the Contracting Officer Representative (COR), Chief, Chemical Handling and Data Analysis Branch, Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR).

The overall objective of this project, a continuation of one that started in 1966, was 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 of interest to the USAMRMC Drug Development Program for parasitic and infectious diseases, chemical and biological defense, anti-viral studies, etc. Specific objectives were to: design, develop, validate, and execute methods to determine the following characteristics of candidate bulk pharmaceutical substances and formulated drugs:

- Identity, purity, and strength.
- Stability.
- Other physical and chemical characteristics, including weight variation, content uniformity, and other such compendial requirements.
- Qualitative and quantitative identity of impurities.
- Special projects not covered by the above headings.

FINAL REPORT

Sample Analyses

During the contract period, 1 August 1991 to 30 June 1997, analyses of the following samples were completed and the reports sent to the COR.

1. WR302AG, BM11449; -AH, BM11458, p-aminopropiophenone, bulk assays, Report No. 768.
2. WR448AG, AG28874; -BB, AX09212; -BC, AY38994; -BD, AY39000; and -BH, BN34670; dapsone, semi-quantitative assays, Report No. 842.
3. WR2976AY, AW23860; and -CJ, BN34885; quinine sulfate, semi-quantitative assays, Report No. 836.
4. WR3091AG, BN34894; and -AC, AG64932, proquanil hydrochloride, semi-quantitative assays, Report No. 843.
5. WR6026AK, BM10399 (placebo) and -AL, BM10460 (active, 30 mg/capsule), 6-methoxy-8-(6-diethylaminohexylamino)lepidine dihydrochloride, Report Nos. 748 and 750; -AL, BM10460, capsule assay, Report No. 811; -AF, BK01845, bulk assay, Report No. 847; -AM, BN39246; -AN, BN39225; -AP, BN39264, capsules assays, Report No. 856; -AQ, BN42485; -AR, BN42494; and -AS, BN42501, capsules assays, Report No. 868; -AL, BM10460; -AH, BM03983, -AJ, BM03992; -AR, BN42494, capsules assays, Report No. 879; -AT, BN61695, capsule assay, Report No. 881; BN20201, lot EG101196, bulk assay, Report No. 906; -AQ, BN42485, capsule assay, Report No. 926; -AR, BN42494, capsule assay, Report No. 927; -AS, BN42501, capsule assay, Report No. 928.
6. WR6798AL, AF50013; -AT, BN34689; -AM, -AT68417; and -AM, ZP19685, diformyl dapsone, semi-quantitative assay, Report No. 844.
7. WR7557AP, BB59190; -AX, BN34849; -AZ, BN34858; and -BA, BN34876, sulfadiazine, semi-quantitative assay, Report No. 837.
8. WR35928AQ, BM08915, O-2-amino-2-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-[O-2,6-diamino-2,6-dideoxy- β -L-idopyranosyl-(1 $\rightarrow$ 3)- β -D-ribofuranosyl-(1 $\rightarrow$ 5)]-2-deoxy-D-streptamine sulfate (paromomycin sulfate cream), formulation assay, Report No. 753; -AR, BM12053, paromomycin sulfate, bulk assay by pre-column derivatization with 2,4-dinitro-1-fluorobenzene (DNFB), Report No. 772; -AR, BM12053, paromomycin sulfate, bulk assay using an OPA derivatization, Report No. 780; -AV, BM17861, paromomycin sulfate,

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assay, Report No. 825; -AV, BM17861, paromomycin and WR73633AE, BM18591, gentamicin recovery studies, Report No. 834.

9. WR46234AY, BM08782 (1% w/v active) and -AZ, BM08791 (placebo), 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (niclosamide), Report No. 743; -BA, BM09994 (active, 1%), and -BB, BM10004 (placebo), formulation assay, Report No. 754; -BC, BM11412 (active, 1%), and -BB, BM11421 (placebo), formulation assay, Report No. 764; -BF, BM13710 (active, 1%), niclosamide, formulation assay, Report No. 773; -AE, BM13569 (placebo), Report No. 781; -BC and -BF, BM11412 and BM13710, Topical anti-penetrant (TAP), assay, Report No. 830.
10. WR73633AE, BM18591, gentamicin sulfate, assay, Report No. 827.
11. WR100553, BN71271, doxycycline hyclate, bulk assay, Report No. 905.
12. WR142490BL, BM04391 (250 mg/tablet), erythro- α -(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride (mefloquine), Report No. 742; -BQ, BM13774 and -BR, BM13783, tablet formulation assays, Report No. 774; -BS, BM18368, assay, Report No. 845.
13. WR150197AC, BM15867, antipyrine, capsule assay, Report No. 810.
14. WR171669AU, BM01792, halofantrine, bulk assay, Report No. 860; -AY, BM01792, 250-mg tablet assay, Report No. 884.
15. WR178460AC, BM08577, desbutylhalofantrine hydrochloride, bulk assay, Report No. 880; -BN78716, lot JEF-28030-36, bulk assay, Report No. 912; chromium content determination, Report No. 931.
16. WR229870AP, BM18386, formulated sodium stibogluconate injection solution (Pentostam), assay development and assay, Report No. 828.
17. WR233602AH, BM11243, floxacrine, bulk assay; Report No. 761.
18. WR238605AK, BM13050, N⁴-(2,6-dimethoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)-8-quinolinyl)-1,4-pentanediamine succinate, bulk assay, Report No. 765; -AC, BK73252, re-evaluation of purity, Report No. 767; -AJ, BM12562, bulk assay, Report No. 775; -AL, BM16668, -AM, BM16677 and -AN, BM16686, capsule assays, Report No. 806; -AP, BN38552, capsule assay, Report No. 853; -AQ, BN38543, placebo assay, Report No. 853; -AN, BM16686, tablet assay, Report No. 883; -AR, BN64016, bulk assay, Report No. 885; -AS, BN64025, bulk assay, Report No. 893; -AT, BN65479, capsule assay, Report No. 896; -BN69897, lot 08910496, capsule assay, Report No. 903; -BN69904, lot 08810496, placebo assay, Report No. 903; -AU, BN69548, bulk assay, Report No. 902; -BN85640, bulk assay, Report No. 920; -BN86825, capsule assay, capsule dissolution, and capsule disintegration

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studies, Report No. 921; -BN86834, placebo assay, Report No. 922; -BN85640, Ash Stevens lot no. DJD-15-93, succinate assay, Report No. 933.

19. WR-242511AF, BM19356, 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate, assay, Report No. 829; -AE, BM05618, physical characterization, Report No. 887; -AF, BM19356, physical characterization, Report No. 888.
20. WR243251AB and -AC, BJ45753 and -BL21100, 7-chloro-3-(2,4-dichlorophenyl)-1-[(3-dimethylamino)propyl]imino}-1,2,3,4-tetrahydro-9(10H)acridone, assays, Report Nos. 832 and 833.
21. WR249655AN, BM17567, 1-(2-hydroxyiminomethyl-1-pyridino)-3-(4-carbamoyl-1-pyridino)-2-oxapropane dichloride monohydrate (HI-6-H₂O), bulk assay, Report No. 813; -AQ, BM18377, assay, Report No. 824; -AR, BN44621, assay, Report No. 871.
22. WR250710BF, BN39808, lot no. 32053 & -BG, BN39817, lot no. 105525 (30 mg/tablet), and -BH, BN41077, lot no. C181554-01 (placebo), 3{[(dimethylamino)carbonyl]oxy}-1-methylpyridinium bromide, assay, dissolution and disintegration, Report No. 862 and amendment; -BJ, BN51162, lot no. 94-083, bottle A (30 mg/tablet), assay, Report No. 876.
23. WR253997AH, BM11609, lot no. JN16-85-2, dihydroartemisinin, assayed for particle distribution, Report No. 802.
24. WR255663AK, BM04131, artelinic acid, bulk assay, Report No. 703.
25. WR256283AC, BM15858, α -artesianic acid, bulk assay, Report No. 807; -AD, BM17174, Batch NJ1-39-4, Report No. 812.
26. WR258948AC, BM11207 and -AD, BM11216, p-aminooctanophenone, bulk assay, Report No. 769.
27. WR268172AB, BM08871, 3-(4-carbamoyl-1-pyridino)-1-(2,4-bis(hydroxyiminomethyl)-1-pyridino)-2-oxapropane dimethanesulfonate; and -AC, BM10406, the dichloride, physical characterizations and comparison, Report No. 757.
28. WR268380AD, BM04506 and -AE, ZP65589, thiotaurine; -AF, BM05049, thiotaurine sodium salt, assay, Report No. 746.
29. WR268970AB, BM09261, 3-deazaneplanocin A hydrochloride hemihydrate, assay, Report No. 745.

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30. WR269410AB, BM11565 and -AC, BM11574, p-aminoheptanophenone, bulk assay, Report No. 770.
31. WR272677AC, BM17076, p-hydroxylaminoheptanophenone, bulk assay, Report 804.
32. WR279396AB, lot no. WRAST02-41A, paromomycin and gentamicin freebases in cream formulation; -AC, lot no. WRAST02-41B, placebo, assay, Report Nos. 851 and 858; -AD, BN39675, active; -AE, BN39684, placebo, assay, Report No. 859; -AF, BN42985, active; -AG, BN42994, placebo, assay, Report No. 866; -AH, BN64230, assay, Report No. 886; -AK, BN64258, assay, Report No. 891; -AH, BN64230, assay, Report No. 894; BN85873, assays, Report Nos. 923 and 924; BN85864, placebo, assay, Report No. 925; BN85622, assays, Report Nos. 938 and 939; BN85631, assay, Report No. 940. A study on recovery of paromomycin and gentamicin from Formulation 232, Report No. 834.
33. Microencapsulated of colonization factor antigen (CFA) vaccine, Report No. 821. During the report period, a colorimetric protein assay based on complexation between bicinehoninic acid and cuprous ion, which results from reduction of cupric ion by a protein, was developed. The assay and its several refinements were applied to more than a hundred samples of microencapsulated CFA vaccine material to determine their protein contents. Additionally, the acetonitrile, heptane, and sucrose contents in the microspheres were also determined. Moreover, the proteins in some of these samples were also characterized by electrophoresis. These analyses were performed for Col. Robert Reid of the Department of Gastroenterology, with authorization from the Project COR.

Stability and Solubility Studies

Stability and solubility studies on the following samples have been completed and their reports submitted to the COR.

1. WR6026AF, BK01845, 6-methoxy-8-(6-diethylaminohexylamino)lepidine dihydrochloride, shelf-life, 8-year sampling, Report No. 736; 9- and 10-year samplings, Report No. 792.
2. WR6241BE, BM06662, Duphar atropine autoinjectors, accelerated stability study, 35°, 50° and 60 °C, Report No. 759; 35° accelerated stability, 2-year sampling, Report No. 798; 39-week sampling, Report No. 815.
3. WR35928AQ, BM08915, paromomycin cream, stability studies at 25°, 35°, and 45 °C, Report No. 753.
4. WR46234AU, BM08139, 1% w/v solution and AV, BM08148, placebo solution, 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (niclosamide), stored at 35°, 45° and 55 °C, Report No. 739; AJ, BL44970, JD-10-58, 51-month sampling, Report No. 744; 5-year sampling, Report No. 783; BC, BM11412; room-temperature stability study with camouflage paint (MIL-P-2019F, lot No. G-016) and sun screen lotion (NSN6505-01-121-

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2336), Report No. 766; BF, BM13710, cold-temperature stability, -20° to 4° to RT, RT to 4° to -20°, and -20° to RT to 4°, Report No. 782; BF, BMd13710, topical anti-penetrant (TAP), cold-temperature stability, Report No. 849.

5. WR142490AU, BK11592, erythro- α -(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinoline methanol hydrochloride (mefloquine hydrochloride), 9-year shelf life stability, Report No. 779; 10-year sampling, Report No. 793; AV, BK62900, Code No. 6505-01-107-1480, Lot No. C121133-02, 250 mg/tablet, shelf life, 8-year sampling, Report No. 786; AW, BL09613, Code No. 6505-01-107-1480, Lot No. C123173-01, 250 mg/tablet, shelf life, 6-year sampling, Report No. 787; AX, BL18210, shelf life, 5-year sampling, Report No. 788; -BL, BM04391, shelf life, 26-month sampling, Report No. 789; AV, BK62900, 10.5-year shelf-life sampling, Report No. 848.
6. WR171669AS, BL56676, 1,3-dichloro-6-trifluoromethyl-9-[1-hydroxy-3-(di-n-butylamino)propyl]phenanthrene hydrochloride (halofantrine hydrochloride), 3-year shelf-life sampling, Report No. 790; 4-year shelf-life sampling, Report No. 803; 6-year shelf-life sampling, Report No. 870; 7-year shelf-life sampling, Report No. 899; 8-year shelf-life sampling, Report No. 930.
7. WR178460, BM08577, desbutylhalofantrine hydrochloride, solubility and stability in PEG/HOH, Report No. 880; time zero shelf-life sampling, Report No. 916; 3-month shelf-life sampling, Report No. 929.
8. WR238605AG/AH, BM08200 and BM08219, N⁴-(2,6-dimethoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)-8-quinolinyl)-1,4-pentanediamine, succinate, shelf life, 6-month sampling, Report No. 760; 18-month sampling, Report No. 800; 2-year sampling, Report No. 820. WR-238605AC, BK73252, shelf life, 8-year sampling, Report No. 771; 9-year sampling, Report No. 808; AH, BM08219, 4-year shelf-life sampling, Report No. 898.
9. WR242511AE, BM05816, 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate, shelf life, 3- and 6-month samplings, Report No. 738; 9-, 12-, 18-months samplings, Report No. 776; 2-year sampling, Report No. 801; 3-year sampling, Report No. 835; 4-year sampling, Report No. 877; 5-year sampling, Report No. 892; 6-year sampling, Report No. 917; a room-temperature (RT) stability study of WR242511 in water, Report No. 900; RT stability studies of lot AE suspended in water/methylcellulose/Tween 80 (W/M/T) and in saline; Report No. 897; a 4° C stability study of lot AE suspended in (W/M/T), Report No. 910.
10. WR249655AC, BK38655, 1-(2-hydroxyiminomethyl-1-pyridino)-3-(4-carbamoyl-1-pyridino)-2-oxapropane dichloride monohydrate (HI-6·H₂O), shelf life, 8-year sampling, Report No. 740; 9- and 10-year samplings, Report No. 794; -AM, BM08862 and -AP, BM16659, HI-6 chloride and mesylate, bulk solubilities and solution stabilities in water, Report No. 826.
11. WR250710BB, BM03509, Lot No. 038641, 30 mg/tablet, pyridostigmine bromide, accelerated stability studies at 35°, 50°, and 60 °C for one year, Report No. 749; at 35 °C for

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two years, Report No. 784; at 35 °C for two years and two months, Report No. 797; at 35 °C for two years and eight months, Report No. 816. -AF, BK75309, Control Nos. WRA-23-12196F (22 mg/tablet) and WRA-24-12226S (22 mg/tablet), shelf-life stability, 49-month samplings, Report No. 752; 62 month samplings, Report No. 785. WR-250710BB, BM03509, Lot No. 038641, 30 mg/tablet, RT stability, 17-month sampling, Report No. 751; 26-month sampling, Report No. 762; 31-month sampling, Report No. 796; 37-month sampling, Report No. 817; 44-month sampling, Report No. 831; 69-month sampling, Report No. 895; 84-month sampling, Report No. 935.

12. WR253997AH, BL51037, dihydroartemisinin; bulk solubility in 13 media, Report No. 802.
13. WR255131AB, BL19226, Lot No. SA-100386/030B, β -arteether, 4-year sampling, Report No. 737; 5-year sampling, Report No. 795; 6-year sampling, Report No. 818.
14. WR255663AK, BM04131, 4-(10'-dihydroartemisininoxymethyl)benzoic acid hemihydrate (artelinic acid), shelf-life stability study: 1-year sampling, Report No. 741; 1.5- and 2-year samplings, Report No. 778; 3-year sampling, Report No. 823; 4-year sampling, Report No. 857; 5-year sampling, Report No. 882; 6-year sampling, Report No. 907. A room-temperature solubility and stability study, Report No. 875.
15. WR268172AB, BM08871, 3-(4-carbamoyl-1-(2,4-bis(hydroxyiminomethyl)-1-pyridino)-2-oxapropane dimethanesulfonate and AC, BM10406, the dichloride, solubility study and comparison, Report No. 757.
16. WR268876AA, BM06653, Mark I, atropine portion of 2-PAM/atropine autoinjector kit, Lot 0T5066 accelerated stability study, 35°, 50° and 60 °C, 44- to 47 week-samplings, Report No. 747; -AA, AM06653, atropine injectors, Lot OS4056, accelerated stability studies at 35°, 50°, and 60 °C, 56-week samplings, Report No. 758; 35°, 111-week sampling, Report No. 799; 35°, 139-week sampling, Report No. 815.
17. WR269410AB, BM11565, p-aminopropiophenone; bulk solubility, Report No. 805; -AC, BM11574, RT and accelerated stability studies at 35°, 45° and 55 °C, Report No. 777; -AB, BM11565, solubility study, Report No. 805.
18. WR272677AB, BM15214, p-hydroxylaminoheptanophenone, bulk stability and solution stability study, Report No. 804.
19. WR279396AF, BN42985, an accelerated stability study on a cream formulated with paromomycin and gentamicin, Report No. 874; -AH, BN64230, a stability study on a cream formulation stored at 4°C, time 0 sampling, Report No. 901; 3-months sampling, Report No. 908; 6-months sampling, Report No. 914; 12-months sampling, Report No. 934.
20. WR279435AA, -AB, and -AC, sodium thiosulfate injection solutions, 12.5g/50 mL, Lot Nos. 85146, 85147, and 85148, shelf-life stability, 7-year samplings, Report No. 791; 7-year and 10-month samplings, Report No. 819.

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21. WR279436AA, -AB, and -AC, sodium nitrite injection solutions, 300 mg/10 mL, Lot Nos. 85186, 85187, and 85188, shelf-life stability, 6.5-year samplings, Report No. 763.

Chiral Separations

Chiral separations on the following samples have been completed and the reports have been sent to the project COR.

1. WR238605AC, BK73252, N-(2,6-dimethoxy-4-methyl-5-(3-(trifluoromethyl)phenoxy)-8-quinoliny)-1,4-pentanediamine succinate, and its R-(-)- and S-(+)-((4-amino-1-methylbutyl)amino)2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline fumarate, WR280407AA, BN57422 and WR280408AA, BN57431, chiral separation and circular dichroism determinations, Report No. 909.
2. WR242511AF, BM19356, 8-((4-amino-1-methylbutyl)amino)-5-(1-hexyloxy)-6-methylquinoline DL tartrate, chiral separation, Report No. 888.
3. WR243251, 7-chloro-3-(2'',4''-dichlorophenyl)-1-((3'-(dimethylamino)propyl)imino)-1,2,3,4-tetrahydro-9-(10H)acridone, chiral separation, Report No. 915.
4. WR250547, [R]-7-chloro-3-(2'',4''-dichlorophenyl)-1-((3'-(dimethylamino)propyl)imino)-1,2,3,4-tetrahydro-9-(10H)acridone and the [S]-enantiomer, chiral separation, Report Nos. 904 and 919.

Method Validations

Validations of assay procedures for the following compounds and their formulated products have been completed and the validation reports have been sent to the project COR.

1. WR6026, 6-methoxy-8-(6-diethylaminohexylamino)lepidine dihydrochloride, bulk drug and formulated drug product, Report No. 865.
2. WR35928AV, BM17861, paromomycin sulfate, Report No. 838; and sulfate assay addendum, Report No. 839.
3. WR73633, gentamicin sulfate, Report No. 841.
4. WR142490AU, BK11592, erythro- α -(2-piperidyl)-2,8-bis-(trifluoromethyl)-4-quinolinemethanol hydrochloride (Mefloquine HCl), Report No. 889.
5. WR171669, halofantrine, Report No. 869.
6. WR178460, BM08577, desbutylhalofantrine, chemical assay validation, Report No. 873; chiral separation validation, Report No. 918.
7. WR238605, Report No. 890; C-E-based assay for succinate validation, Report No. 932.

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8. WR242511, 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate, Report No. 878.
9. WR243251, racemic 7-chloro-3-(2'',4''-dichlorophenyl)-1-{{[3'-(dimethylamino)propyl]imino}-1,2,3,4-tetrahydro-9-(10H)acridone, validation of chiral assay, Report No. 915.
9. WR250547, [R]-7-chloro-3-(2'',4''-dichlorophenyl)-1-((3'-(dimethylamino)propyl)imino)-1,2,3,4-tetrahydro-9-(10H)acridone, chiral separation validation, Report No. 904; WR250548, (S)-enantiomer, chiral separation validation, Report No. 919.
10. WR250710, pyridostigmine bromide, Report No. 864.
11. WR255663, artelinic acid, Report No. 872.

Reference Sample Preparation

A reference sample for the following compound has been established.

WR35928, BM17861, paromomycin sulfate, established as an independent reference standard, Report No. 856.

Standard Operating Procedures (SOPs)

During the entire project report period, 55 SOPs were updated.

Presentations

The following presentations have been made.

1. A poster on the room-temperature solution stability of WR-272677, p-hydroxylaminoheptanophenone was presented at the 1993 Medical Defense Bioscience Review Conference held in Baltimore, MD.

Abstract: WR272677 has protected mice against cyanide challenge at the Battelle Laboratory. Single dose oral and intravenous pharmacokinetic and pharmacodynamic studies performed in the division of Experimental Therapeutics at the Walter Reed Army Institute of Research have shown this compound to be a potent former of methemoglobin, or ferrihemoglobin, which selectively binds cyanide. One of the steps in the development of this anticyanide agent is to determine its solubility and solution stability.

The apparent room-temperature solubilities of WR272677AB in aqueous media, ethanol, polyethylene glycol (PEG) 400, and aqueous ethanol have been determined. WR272677 is insoluble (<0.1 mg/mL) in the aqueous media and aqueous ethanol, but is freely soluble (≈ 400 mg/mL) in either ethanol or PEG 400.

WR272677AB dissolved in ethanol or PEG 400 under ordinary atmospheric conditions rapidly decomposes, mainly to p-azoxyheptanophenone. In the absence of molecular oxygen, however, ethanol solutions of WR272677 are stable for at least 24 hours.

2. A poster on a determination of bis(chloromethyl) ether (BCME) in bulk HI-6 was presented at the 1996 Medical Defense Bioscience Review held in Baltimore, MD.

Abstract: A specific, sensitive method for determining trace quantities of BCME in a solid matrix has been developed and validated. Under standard conditions, the lower quantifiable level is < 0.5 nanogram BCME. When the method was applied to bulk samples of HI-6, no measureable amount of BCME could be found, unless the sample was anhydrous. Although BCME is formed from HI-6 even at room temperature, the rate is very slow, and the BCME that is formed is hydrolyzed by the water in the sample. Rate information on BCME formation from anhydrous HI-6 at four temperatures have been determined; from this information, the formation of BCME over time/temperature can be estimated.

Publications

The following publications have resulted from the performance of this contract.

1. "A Chemical Assessment and HPLC Assay Validation of Bulk Paromomycin Sulfate", by Lori L. Olson, John Pick, William Y. Ellis, and Peter Lim, was published in Journal of Pharmaceutical and Biomedical Analysis, 15 (1997) 783-793.

Abstract: This paper describes the compositional analyses of four paromomycin sulfate samples and features a validated HPLC assay method that relies on the fluorescence detection of isoindole derivatives of paromomycin, formed by post-column reaction with *o*-phthalaldehyde and 2-mercaptoethanol.

2. "Development and Validation of A Method to Extract and Quantitate Paromomycin and gentamicin from An Aquaphilic® Cream Formulation" by John Pick, Lori L. Olson, William Y. Ellis, and Peter Lim has been accepted for publication in Journal of Pharmaceutical and Biomedical Analysis, in December 1996.

Abstract: Butanol and dilute sulfuric acid were used to extract paromomycin and gentamicin from Aquaphilic®-based formulated creams. The extraction procedure was validated over different antibiotic concentration ranges for linearity, precision, accuracy, limited specificity, sensitivity and solution stability.

ORIGINAL

Personnel

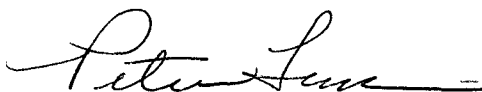
A listing of personnel who received major contract support is as follows:

Peter Lim, P.I.
Lori Olson, Assistant P.I.
Robert Petesch, Chemist
Lee D. Nguyen, Chemist
John Pick, Chemist
Tina Nguyen, Chemist
Shane Ridge, Chemist
Gwen Wilkins, Secretary

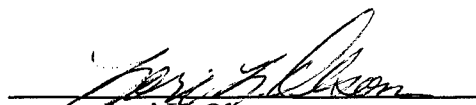
Summary/Conclusion

During the entire contract period, 125 samples of bulk drugs and dosage formulations were analyzed for identity, purity or potency; 133 samples were studied for stability and solubility. Four chiral separation methods were developed and validated, and 11 other assay methods were validated. Special projects included the development and application of assays for determining protein content, residual solvents, and other components in microsphere vaccine preparations. A second special project was the development and application of an assay for determining BCME in HI-6 bulk drugs. Poster presentations were made at the 1993 and the 1996 Bioscience Reviews. One publication appeared in press and a second has been accepted for publication.

Respectfully submitted,



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DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y)

10 Aug 98

MEMORANDUM FOR Administrator, Defense Technical Information
Center, ATTN: DTIC-OCF, Fort Belvoir,
VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for the following contracts. Request the limited distribution statement for these contracts be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

Contract Number

Accession Document Number

DAMD17-91-C-1020	ADB187724 +✓
DAMD17-92-C-2053	ADB196427 +
DAMD17-94-C-4022	ADB190750 †
DAMD17-94-C-4023	ADB188373 †
DAMD17-94-C-4027	ADB196161 †✓
DAMD17-94-C-4029	ADB190899 †
DAMD17-94-C-4039	ADB188023 †
DAMD17-94-C-4024	ADB189184 †
DAMD17-94-C-4026	ADB187918 †
DAMD17-94-J-4250	ADB221970
DAMD17-94-J-4250	ADB230700
DAMD17-96-1-6241	x ADB233224
DAMD17-96-1-6241	ADB218632 ✓
DAMD17-94-J-4496	x ADB225269
DAMD17-94-J-4392	ADB225308 ✓
DAMD17-94-J-4455	ADB225784 ✓
DAMD17-94-J-4309	ADB228198 ✓
DAMD17-91-C-1135	ADB233658 ✓
DAMD17-94-J-4038	ADB232313
DAMD17-94-J-4073	ADB222794
DAMD17-94-J-4131	ADB219168
DAMD17-94-J-4159	ADB232305
MIPR- 95MM5535	ADB232218
95MM5605	ADB233374
95MM5673	ADB226037

MCMR-RMI-S

SUBJECT: Request Change in Distribution Statement

2. Point of contact for this request is Ms. Judy Pawlus at
DSN 343-7322 or email: judy_pawlus@ftdetrck-ccmail.army.mil.

FOR THE COMMANDER:


PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management