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The timely and efficient execution of the U.S. Army Medical Materiel Pharmaceutical Development Program requires a thorough knowledge of regulations issued by the U.S. Food and Drug Administration. In order to accomplish the execution of this drug development program, the Pharmaceutical Systems Project Management Office, an element of the U.S. Army Medical Materiel Development Activity (USAMMDA), awarded a multi-year contract to Engineering and Economics Research (EER) and its subcontractor, Oxford Research International Corporation (ORIC). The EER/ORIC team has provided the necessary managerial and technical expertise to complete the preparation and assembly of IND/NDAs. A total of 9 tasks and 12 subtasks were submitted to the contractor during the first contract year. All task orders were completed or are in progress within the projected delivery schedule and cost estimate.

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DRUG REGULATORY AFFAIRS

ANNUAL REPORT

ARTHUR M. HOROWITZ

JULY 15, 1987

Supported by

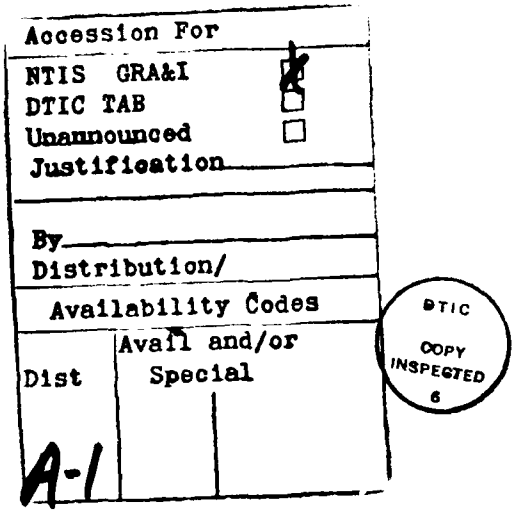
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5009

Contract No. DAMD17-86-C-6189

Engineering and Economics Research Inc.
20251 Century Boulevard
Germantown, Maryland 20874

FOREWORD

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.



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1. Introduction

The Pharmaceutical Systems Project Management Office (PSPMO), an element of the U.S. Army Medical Materiel Development Activity (USAMMDA) holds the responsibility for planning, organizing, directing and controlling all aspects of drug development. Every stage of drug development must be in compliance with current FDA requirements. The principal objective of this contract is to prepare and assemble drug-specific, FDA-related documentation as well as a data management system to track the status of regulatory documentation. The contractor has furnished the necessary personnel, facilities, equipment and supplies to complete the scope of work as prescribed in each task order. In accordance with Section F of the Drug Regulatory Affairs contract, quarterly reports describing the technical progress and financial status for each Task Order have been submitted. This initial Annual Report describes the work performed by the contractor for the 12 month period of June 2, 1986 to June 30, 1987. Keywords: Pharmacology, Management Planning and Control, Synthesis (Chemistry). (AW)

2. Discussion

2.1 Task 86-01 Project Planning, Coordination and Integration

Task 86-01 requires the development and maintenance of a planning, coordinating and task integration infrastructure for the Drug Regulatory Affairs Contract. This infrastructure provides for overall project planning and tracking, individual task planning, monthly project review meetings, quarterly progress reports and attendance at relevant professional meetings and symposia. A recent modification to this task requests the preparation of monthly progress reports.

2.1.1 Overall Project Planning and Tracking

A cost and schedule tracking system has been developed by EER to assist in the preparation of monthly, quarterly and annual reports. An inventory control system to account for property purchased under the subject contract, but for which the government retains property, has been implemented.

A central filing system has been established for all DRA-related documents. The file is maintained in the DRA library.

2.1.2 Individual Task Planning

Nine new task orders were received from USAMMDA during this contract term. Four modifications to the existing task orders were approved. The individual task orders and date these tasks were approved by the contracting officer are summarized as follows:

Task Order	Date Task Order Approved
Task 86-01	July 2, 1986
Task 86-01, Modification 1	May 29, 1987
Task 86-02	July 8, 1986
Task 86-02, Modification 1	January 23, 1987
Task 86-02, Modification 2	April 7, 1987
Task 86-03	July 18, 1986
Task 86-03, Modification 1	June 11, 1987
Task 86-04	August 26, 1986
Task 87-01	December 15, 1986
Task 87-02	November 4, 1986
Task 87-03	December 4, 1986
Task 87-04	December 4, 1986
Task 87-05	March 26, 1987

Approval of Task 87-05, Modification 1, which was submitted to USAMMDA on June 25, 1987, is currently under USAMMDA review.

2.2 Task 86-02 Preparation of Annual IND Progress Reports

This task requires the preparation of annual progress reports on outstanding IND Submissions. The following 15 INDs were identified on June 18, 1986 as requiring the preparation of an annual report:

IND No.	Drug (IND Title)
5,509	Phosphorothioic Acid (WR 2,721)
8,990	Mefloquine (WR 142,490)
9,847	Halofantrine (WR 171,669)
12,735	Enpiroline (WR 180,409)
13,487	WR 194,695
26,740	Ketoconazole (WR 248,310)
17,326	Phosphorothiate (WR 638)
21,084	Antileshmanial (WR 6,026)
23,509	Pyridostigmine (WR 270,710)
27,503	Atropine Sulfate, USP
14,150	Pentostam (WR 229,870)
13,518	Antishock Agent (WR 149,024)
14,252	Temefos
28,301	Atropine and Pralidoxime Chloride
16,666	Ribavirin

2.2.1 Task 86-02, Modification #1

This Task Order requires an evaluation of all existing data, information and other pertinent material relating to oral pyridostigmine (IND 25,509).

2.2.2 Task 86-02, Modification #2

This Task Order, consisting of ten subtasks, requires the collection and evaluation of data and preparation of annual IND progress reports.

2.2.2.1 Ketoconazole.

This subtask requires the preparation of an assessment report and an annual IND progress report for ketoconazole (IND 26,740; WR 248,310).

2.2.2.2 Phosphorothioic Acid.

This subtask requires the duplication and filing of Supplement #9 in the DRA library (IND 5,509; WR 2,721).

2.2.2.3 Mefloquine.

This subtask requires the analysis of three clinical studies comprised of 426 patients who participated in these clinical studies; preparation of three clinical summary reports; and incorporating these reports in the annual IND progress report (IND 8,990; WR 142,490).

2.2.2.4 Halofantrine.

Upon receipt of the bioavailability report from WRAIR, this subtask requires the preparation of the annual IND progress report for IND 9,847; WR 171,669.

2.2.2.5 Enpiroline.

This subtask requires the preparation of an annual IND progress report for IND 12,735; WR 180,409. Clinical data from a study comprised of 162 patients treated with mefloquine or enpiroline will be used in the preparation of this report.

2.2.2.6 Antileishmanial.

This subtask requires the analysis of a pharmacokinetic study and preparation of an annual IND progress report (IND 21,084; WR 6,026).

2.2.2.7 Pentostam.

This subtask requires the collection, duplication and analysis of clinical data from 43 patients as well as preparation of an annual IND progress report (IND 14,150; WR 229,870).

2.2.2.8 Temefos.

The COR advised EER that a letter report does not have to be prepared.

2.2.2.9 Atropine Sulfate, USP.

This subtask requires the preparation of an annual IND progress report (IND 27,503).

2.2.2.10 Atropine 2-PAM.

This subtask requires the preparation of an annual IND progress report (IND 28,301).

2.3 Task 86-03 Preparation of an NDA for Ribavirin (BPL #120)

This task requires the collection and analysis of preclinical and clinical information for the parenteral formulation of ribavirin, as well as the preparation and submission of an NDA in the format required by 21 CFR 314.50.

2.3.1 Ribavirin NDA Team Meetings

Meetings were held on August 7, October 31, 1986 and February 17, 1987 with representatives of USAMMDA, USAMRIID, Viratek and the EER/Oxford team to review the progress achieved in the preparation of the ribavirin NDA. An additional meeting was held on June 29, 1987 with representatives of USAMMDA, USAMRIID, CDC and EER/Oxford to review the clinical data and proposed clinical indications.

Tentative target dates for completion of sections of the NDA were established on October 31, 1986 and revised at the February 17, 1987 meeting. The projected target dates for the completion of this work are as follows:

April 1, 1987 Submission of the Manufacturing and Controls Section of the NDA to the FDA.

June 1, 1987 Completion of Army review of Preclinical Section of NDA with submission to Oxford of any suggestions for revision.

June 15, 1987 Return of final version of Preclinical Section to U.S. Army for submission to the FDA.

June 1, 1987 Completion of all remaining reports (Korean study and second Chinese study) for Clinical Section with transfer of same to the U.S. Army for final review.

July 1, 1987 Return of Clinical Section to Oxford for final revision, if needed.

July 25, 1987 Oxford sends all remaining sections of the ribavirin NDA to EER for review and submission to U.S. Army.

August 1, 1987 Army submits NDA to FDA.

A meeting was held on June 29, 1987, at USAMMDA to review the clinical data and discuss the proposed clinical indications for the NDA submission. The final outcome of this meeting included recommendations to re-analyze the data with respect to disease severity at the time of patient admission as well as to pool mortality data from the two China Studies. A pre-NDA meeting at the FDA was authorized. Submission of the clinical section will occur after this FDA meeting.

2.3.2 General Description of Ribavirin

Ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a nucleoside consisting of D-ribose attached to a 1,2,4-triazole carboxamide. Ribavirin is active both *in vitro* and *in vivo* against both RNA and DNA viruses. There are several proposed modes of action of ribavirin inhibition of viral replication but it is believed to act primarily as a competitive inhibitor of guanosine in the 5' capping of viral messenger RNA. Ribavirin (Virazole^{R}) is currently respiratory tract infections due to respiratory syncytial virus in infants and children.

2.3.3 Phase I Clinical Studies

(i) Single Dose Oral Administration of ^{14}C-Ribavirin.

A single oral dose of ^{14}C-ribavirin was administered to three healthy male volunteer subjects aged 50, 27, and 28 years and weighing 76.6, 73.1 and 79.8 kg, respectively. Subject 1 received a dose of 3.1 mg/kg and subjects 2 and 3 each received a dose of 2.8 mg/kg. Blood samples and spontaneous voided urine specimens were obtained prior to drug administration and at specified intervals over a period of 72 hours.

The results of this study indicated that, in man, a single oral dose of ^{14}C-ribavirin is rapidly absorbed, gradually concentrated in the red cells and simultaneously eliminated in the urine as ^{14}C-ribavirin, 1,2,4-triazole-^{14}C-3-carboxamide (T-COHN$_2$) and 1,2,4-triazole-^{14}C-3-carboxylic acid (T-COOH).

(ii) Steady-State Pharmacokinetics of Ribavirin Following Oral Administration to Four Human Volunteer Subjects.

In a study of the efficacy and safety of ribavirin in the treatment of experimentally induced Sandfly Fever, a control group of four healthy volunteer subjects (3 males and 1 female) was given ribavirin orally in daily doses of 1200 mg (400 mg every 8 hours) for 8 days.

Ribavirin appears to concentrate in the red blood cells where levels approximately 50-80 times greater than plasma levels were attained. A plateau at approximately 300 to 500 micromoles per milliliter was reached in the red cells after 4 days of drug administration. Clearance of ribavirin from red cells also appeared to be relatively slow; values in excess of 300 micromoles per millimeter were obtained

9 days after completion of ribavirin administration. On day 28, the ribavirin levels in the red cells of the three subjects ranged from 139 to 265 micromoles per milliliter.

(iii) Pharmacokinetics of Ribavirin Following Oral Administration

In the study of ribavirin for the treatment of Lassa Fever that was conducted in Sierra Leone, patients received 1000 mg ribavirin daily by mouth in three divided doses. Plasma samples of four patients in this study were assayed for ribavirin levels. Ribavirin levels ranged from 1.7 to 5.3 micromoles (mean value 3.1 micromoles) per milliliter approximately 2.5 hours after ingestion of an oral dose.

(iv) Pharmacokinetics of Ribavirin Following Intravenous Administration

In the same Lassa Fever study mentioned above, patients were treated with 1000 mg ribavirin intravenously, four times a day during the first 4 days of therapy followed by 500 mg ribavirin intravenously three times a day for an additional 6 days. The mean plasma ribavirin level at the 1000 mg dose in eight patients was 94 micromoles per milliliter (range: 53-83 micromoles) and is the result of a standard multi-dose, multiple-day parenteral therapeutic regimen.

2.3.4 Phase II Clinical Studies

A parenteral formulation of ribavirin was developed and evaluated in volunteers. The efficacy and safety of ribavirin in the treatment of five viral diseases were evaluated in the following studies.

(i) Lassa Fever

Lassa Fever, endemic in West Africa, has a more varied clinical picture ranging from an undifferentiated febrile illness to frank hemorrhagic fever with the capillary leak syndrome and complications such as pleural effusions, pericarditis, hepatitis and eighth nerve deafness. Death occurs in 15 to 20 percent of hospitalized patients. Lassa Fever is caused by a specific virus which is one of three morphologically identical but immunologically distinct Arenaviruses, (the other two are the Machupo virus of Bolivia and the Junin virus of Argentina).

This investigation involved three interdependent clinical studies of Lassa Fever conducted in two rural hospitals in Sierra Leone.

1. A preliminary case-control study of the diagnostic aspects and clinical course of untreated Lassa fever in patients with the disease.

2. A randomized, controlled, parallel-group study (Randomized Study No. 1) to compare the efficacy and safety of ribavirin administered orally (15 mg/kg/day in three doses of 10 days) with the efficacy and safety of one or two units (approx. 4-8 ml/kg) of Lassa convalescent plasma with an antibody titer $\geq$ 1:128 administered intravenously in the treatment of patients with Lassa Fever.

3. The design of this study was a randomized, controlled, parallel-group using either immune plasma or intravenously administered ribavirin, except that patients with documented Lassa Fever who were admitted to the study were required to have an admission AST level $\geq$ 150 IU/L.

These individuals were randomly assigned to one of two treatment groups. One group received a loading dose of 2 gm ribavirin (iv) followed by 1 gm (iv) every 6 hours for 4 days and 0.5 gm (iv) 8 hours for an additional 6 days. The other group received the same ribavirin regimen plus one unit (300 ml) of Lassa convalescent plasma with the first ribavirin dose.

The investigators concluded that ribavirin is effective in the treatment of Lassa Fever and that the risk: benefit ratio for the drug is adequate to warrant initiation of ribavirin treatment at any point in the illness.

(ii) Epidemic Hemorrhagic Fever with Renal Syndrome

Epidemic Hemorrhagic Fever with Renal Syndrome is a collective term applied to a number of geographically diverse but clinically similar viral diseases occurring in Europe, South America, Africa, and northern Asia. These diseases all share in common the clinical features of fever, varying degrees of hemorrhagic manifestations and renal insufficiency. The most important pathological derangement in most hemorrhagic fevers of viral origin is a capillary leak syndrome. Conjunctival infection, dermal hyperemia, edema, bradycardia, and proteinuria lead in a matter of days to hypovolemic shock preceded by petechiae and usually minor hemorrhages from mucous membranes. Epidemic hemorrhagic fever occurring in north China, which carries a mortality rate of 10-30 percent, is nov recognized to be caused by a Bunyavirus recently named Hantaan and is designated the prototype for a new genus-Hantavirus-within the family of Bunyaviridae. Serological and biochemical studies have established that Hantaan virus is antigenically related to other viruses known to be responsible for producing epidemic hemorrhagic fever with renal syndrome. Ribavirin is active <u>in vitro</u> against Hantavirus strains

and in vivo against Hantaan virus in the suckling mouse model. The drug is also effective in rats and rhesus monkeys infected with Rift Valley Fever virus, also a member of the Bunyaviridae.

Two earlier open-labelled studies of ribavirin for the treatment of epidemic hemorrhagic fever were conducted in China. Drug therapy was initiated within five days of the onset of symptoms and given intravenously in doses of 500 mg/day and 700-750 mg/day, respectively, for 3 days each. In both studies, treatment resulted in a significant reduction in the incidence of hypotension and oliguria, the duration of proteinuria and the overall severity of the disease. Similar results were obtained in a more recent double-blind, placebo-controlled study conducted on 180 patients in which ribavirin treatment was initiated within 4 days of the onset of symptoms and was given according to a dosage schedule that provided an initial loading dose of 33 mg/kg followed by 16 mg/kg every 6 hours for 4 days and 8 mg/kg for a subsequent 6 days. Reversible anemia was the only clinically significant adverse reaction attributable to ribavirin.

(iii) Sandfly Fever

Sandfly (phlebotomus) fevers are acute, self-limiting diseases caused by phleboviruses that have the potential to produce debilitating outbreaks of the disease during military operations.

Twelve adult human volunteers (10 males and 2 females; ages 20 to 36 years) were inoculated intravenously with dilute human plasma containing sandfly fever virus. Beginning the following day, six subjects received daily oral doses of 1200 mg ribavirin (400 mg every 8 hours) for 8 days and 6 subjects received matching placebo over the same period of time. A fourth group, comprising one female and 3

male volunteers, received ribavirin only for the purpose of determining the steady-state pharmacokinetics of the drug. All ribavirin-treated subjects remained asymptomatic throughout the study. Four of the 6 placebo controls became ill with symptoms of fever, chills, myalgia, prostration and headache that persisted for 3 days.

The conclusion reached by the investigators was that ribavirin prevented clinical disease in subjects inoculated with sandfly fever virus but did not prevent an immunological response to sandfly fever virus exposure.

(iv) Argentine Hemorrhagic Fever

Argentine Hemorrhagic Fever is a severe, debilitating, and often fatal disease caused by the Junin virus, one of three Arenaviruses pathogenic to man. The endemo-epidemic areas for the disease are located in the humid pampa, the richest farmland in Argentina. In man, the clinical picture ranges from a mild flu-like infection to a fulminant disease with a mortality rate of 15-30 percent in untreated patients. Typically, a 7-to-14-day incubation period is followed by fever and generalized gastrointestinal symptoms, including gingival congestion and bleeding. Leucopenia and thrombocytopenia are important manifestations of the disease process and typically alpha-interferon levels are very high. In most patients improvement occurs during the second week, while those with more severe disease develop a hemorrhagic-neurologic shock syndrome which frequently leads to death. Treatment with immune plasma is effective in preventing death provided that it is administered at doses of more than 3000 therapeutic units/kg body weight within 8 days of the onset of symptoms.

This study was conducted at Instituto Nacional de Estudios cobre Virosis Hemmorrhagicas (INEVH), 2700 Pergamino, Argentina.

This was an open-label, single-treatment-group pilot clinical study to evaluate the tolerance and antiviral effect of intravenous ribavirin in patients diagnosed with Argentine Hemorrhagic Fever (AHF) who had symptoms and signs of the disease for more than 8 days.

Ribavirin was administered according to the following 10-day regimen: 34 mg/kg (iv) as a loading dose, followed by 17 mg/kg (iv) every 6 hours for 4 days, and 8 mg/kg (iv) every 8 hours for the subsequent 6 days. Pregnant or nursing women were excluded from participation in the study.

The investigators concluded that in advanced cases of Argentine Hemorrhagic Fever, ribavirin had a clinically useful antiviral effect and that anemia, the only adverse effect observed, was easily controlled.

(v) Congo-Crimean Hemorrhagic Fever

Congo-Crimean Hemorrhagic Fever (CCHF) is endemic and epidemic in the Mideast and in all of Africa except the Sahara Desert. Similar to Epidemic Hemorrhagic Fever of north China and Asia, this disease is caused by a member of the Bunyaviridae group. CCHF may present in various degrees of severity, ranging from a mild febrile condition to a severe disorder accompanied by all of the characteristics of a viral hemorrhagic fever, including a high mortality rate. CCHF, in common with Lassa Fever, is often associated with an icteric form of hepatitis which, in itself, is not a primary cause of death.

The study was conducted at the Tygerberg Hospital, near Capetown in the Republic of South Africa. Sixteen high-risk patients were diagnosed with the disease and admitted to a special isolation ward for observation and possible treatment. Eight of these individuals were subsequently reclassified as very-high-risk patients warranting prophylactic treatment for CCHF. Six of these 8 patients received ribavirin as an initial intravenous bolus dose of 45 mg/kg with subsequent total doses ranging from 8.2 grams over a period of 4 days to 20 grams for an additional 8 days. Three of the 6 individuals also received a single bolus dose of interferon. However, this form of treatment was discontinued, due to the appearance of apparent adverse reactions of an allergic nature. One individual received hyperimmune serum.

Of the 6 subjects treated prophylactically with intravenous ribavirin only one developed evidence of CCHF and this occurred only in a mild form, without any evidence of hemorrhagic manifestations. The five subjects classified as very high risk did not develop CCHF or evidence of antibodies to the virus. Two high risk subjects who did not receive ribavirin both developed a severe form of CCHF. The investigators concluded that there were insufficient data to evaluate the effectiveness of ribavirin for the prophylaxis of CCHF. Additional clinical studies were recommended.

2.4 Task 86-04 Data Management for Document Presentation

This task requires the development and maintenance of a data management system to support the preparation of IND and NDA documents for the Pharmaceutical Systems Project Management Office.

A Zenith AT compatible computer was purchased for this task. A specially configured version of the DRA Document Management Support System which allows searching the data base and printing, but doesnot allow access to the equipment used to add new records or edit existing records, was developed from discussions held with LTC G. Turner and Mr. Robert Harshman on 27 January 1987. Additional changes and modifications to the complete system were suggested and subsequently implemented. Procedures for system back-up utilizing a 20 megabyte tape cartridge were established. USAMMDA has been provided with a tape of the most current system and data base.

The data management support activities can be summarized as follows:

- A filing subsystem to store hard copies of DRA documents has been set-up. Documents are filed by the IND number and subject.
- A computerized data base containing the information from the cover pages has been established.
- A program has been written which provides a print-out of the document cover pages and a catalog of the library acquisitions.
- Procedures which will ensure updating and maintenance of this data base system have been established.
- A computerized file tracking and control subsystem using a bar code device for check-out and return of documents is operational.
- A subsystem to search and locate documents using the information contained on the cover sheets is available.
- All systems have been integrated and addressed by a menu.

On April 3, 1987, the computerized file tracking and control system for the DRA library was demonstrated at USAMMDA.

2.5 Task 87-01 Halofantrine

The purpose of this task is to determine whether there are adequate data to support an NDA for Halofantrine. This drug is being studied for use in the prophylaxis and treatment of malaria caused by P. falciparum. This report identified both the strengths and weaknesses of the following sections of the NDA: manufacturing and control, pre-clinical and clinical sections.

2.6 Task 87-02 Literature Review of Cholinergic Inhibitors

This task requires the preparation of a literature review on the toxicology resulting from inhibition of acetylcholinesterase on the neuromuscular junction. This review was written for inclusion in Section 6 of the IND. An executive summary of the literature was also prepared for review by a Pyridostigmine Blue Ribbon Committee.

2.7 Task 87-03 Pharmacokinetic Analysis of Atropine

The purpose of this task is to prepare a scientific report for the study: "A Comparative Analysis of the Pharmacokinetic Properties of Intramuscularly-Administered Atropine in Humans and Rhesus Monkeys." This was an open-label comparative study in which each subject received a single intramuscular dose of atropine (0.025 to 0.035 mg/kg for the monkeys and the approximate equivalent dose for humans). The study demonstrated that both species showed relatively similar mean values for peak plasma atropine concentration and for the time after atropine intramuscular administration required to reach this peak. The monkey eliminates atropine from plasma approximately twice as rapidly as man, as evidenced by the lower plasma half-life, the higher mean elimination constant and plasma atropine versus time AUC calculations. The report speculated that

administration of a single dose of atropine in man would result in approximately twice the duration of effective atropine prophylactic activity in man for an equivalent mg/kg dose in the monkey.

2.8 Task 87-04 Pyridostigmine Pharmacokinetic Analysis

The requirements of this task include: (1) Summarization of data on cholinesterase inhibition with descriptive statistics for time and dose; (2) Preparation of a pharmacokinetic report on plasma pyridostigmine levels and a correlation analysis of cholinesterase inhibition and associated plasma pyridostigmine levels.

A comparative bioavailability crossover design study of 18 subjects carried out at a dose level of 30 mg confirmed no significant difference between the tablet and syrup formulation of pyridostigmine.

This open, cross-over clinical study demonstrated that oral administration of pyridostigmine, 0.40 mg/kg to 0.90 mg/kg, produces a proportional increase in RBC acetylcholinesterase inhibition. The 0.40 mg/kg dose (approximately 30 mg) inhibits RBC acetylcholinesterase in the range of 20 to 40 percent. This degree of acetylcholinesterase inhibition is considered to offer optimal protection against nerve gas poisoning.

2.9 Task 87-05 Pyridostigmine Acetylcholinesterase Statistical Study

This task requires the analysis of a pharmacokinetic study conducted in Rhesus monkeys and man to determine the dose effect relationship of pyridostigmine and inhibition of acetylcholinesterase between the two species. The results from this study will be used to support the hypothesis that extrapolation of monkey data to man is valid.

This open cross-over study was conducted in 12 subjects orally treated with 0.40, 0.57, 0.73 and 0.40 mg/kg pyridostigmine syrup. The study demonstrated a large individual variation in the pharmacokinetic response of pyridostigmine in humans and monkeys.

The pyridostigmine plasma AUC is greater in man as compared to monkey. The AUC response for both species was shown to be dose dependent and linear for dose. However, a non-linear relationship was observed with respect to RBC acetylcholinesterase inhibition and pyridostigmine dose. These results appear to indicate that higher doses of pyridostigmine probably would not result in a linear increase in acetylcholinesterase inhibition.

3.0 Status of Accomplishments

A total of 9 tasks and 12 subtasks were submitted to the contractor during this performance period. All tasks/subtasks are proceeding on schedule. The following table summarizes the technical progress for each task/subtask.

SUMMARY TABLE

TASK ORDER TECHNICAL PROGRESS

Task Order	Deliverable	Submission Date	Status of Task Order	Status of Subtask
86-01			in progress	
	1st Quarterly Report	9/15/86		complete
	2nd Quarterly Report	12/15/86		complete
	3rd Quarterly Report	4/15/87		complete
	4th Quarterly Report	7/15/87		complete
	1st Annual Report	7/15/87		complete
	June Monthly Report	7/01/87		complete
86-02			in progress	
	Planning Task	6/18/86		complete
	Planning Task	11/16/86		complete
	Ketoconazole (original)	11/16/86		complete
	Enpiroline (original)	11/16/86		complete
	Pyridostigmine			
	Status Report	5/08/87		complete
	Assessment Report	3/16/87		complete
	Annual IND Progress Report	5/28/87		complete
	Ketoconazole			
	Assessment Report	5/15/87		complete
	Draft IND Amendment Report	6/29/87		gov't review
	Final IND Amendment Report			
	Phosphorothioic Acid			
	Duplicate Supplement #9	5/08/87		complete
	File in DRA Library	5/11/87		complete
	Draft Letter Report			
	Final Letter Report			
	Mefloquine			
	Collect and summarize clinical data			in progress
	Draft IND Amendment Report			
	Final IND Amendment Report			
	Halofantrine			
	Collect and summarize clinical data			in progress
	Draft IND Amendment Report			in progress
	Final IND Amendment Report			

Task Order	Deliverable	Submission Date	Status of Task Order	Status of Subtask
	Enpiroline			
	Collect and summarize clinical data			in progress
	Draft IND Amendment Report			in progress
	Final IND Amendment Report			
	Antileshmanial (WR 6,026)			
	Draft IND Progress Report			in progress
	Final IND Progress Report			
	Pentostam			
	FDA Letter Report	4/09/87		complete
	Duplicate CRF	4/23/87		complete
	Summarize clinical data			in progress
	Draft IND Information Report			
	Draft IND Progress Report			
	Atropine Sulfate, USP			
	Annual Update Letter	4/20/87		complete
	Draft Annual IND Progress Report	5/12/87		complete
	Final Annual IND Progress Report	5/21/87		complete
	Atropine-2PAM			
	Draft Annual IND Progress Report	5/12/87		complete
	Final Annual IND Progress Report	5/21/87		complete
86-03	Ribavirin		in progress	
	Original Administration Subtask	11/16/86		complete
	NDA Preparation			
	Mfg. and Control Section	4/01/87		complete
	Pre-Clinical Section	6/08/87		complete
	Clinical Section			in progress
86-04	Document Management		in progress	
	Subsystem Design	10/07/86		complete
	Track & Control Subsystem	11/06/86		complete
	Documentation Subsystem	11/05/86		complete
	Doc. Repost. Subsystem	11/19/86		complete
	Entry Initial Data	12/07/86		complete
	Complete Filing Subsystem	2/27/87		complete
	Complete File System	2/27/87		complete
	Demonstrate System	4/03/87		complete
	Tape Cartridge Delivery	6/25/87		complete

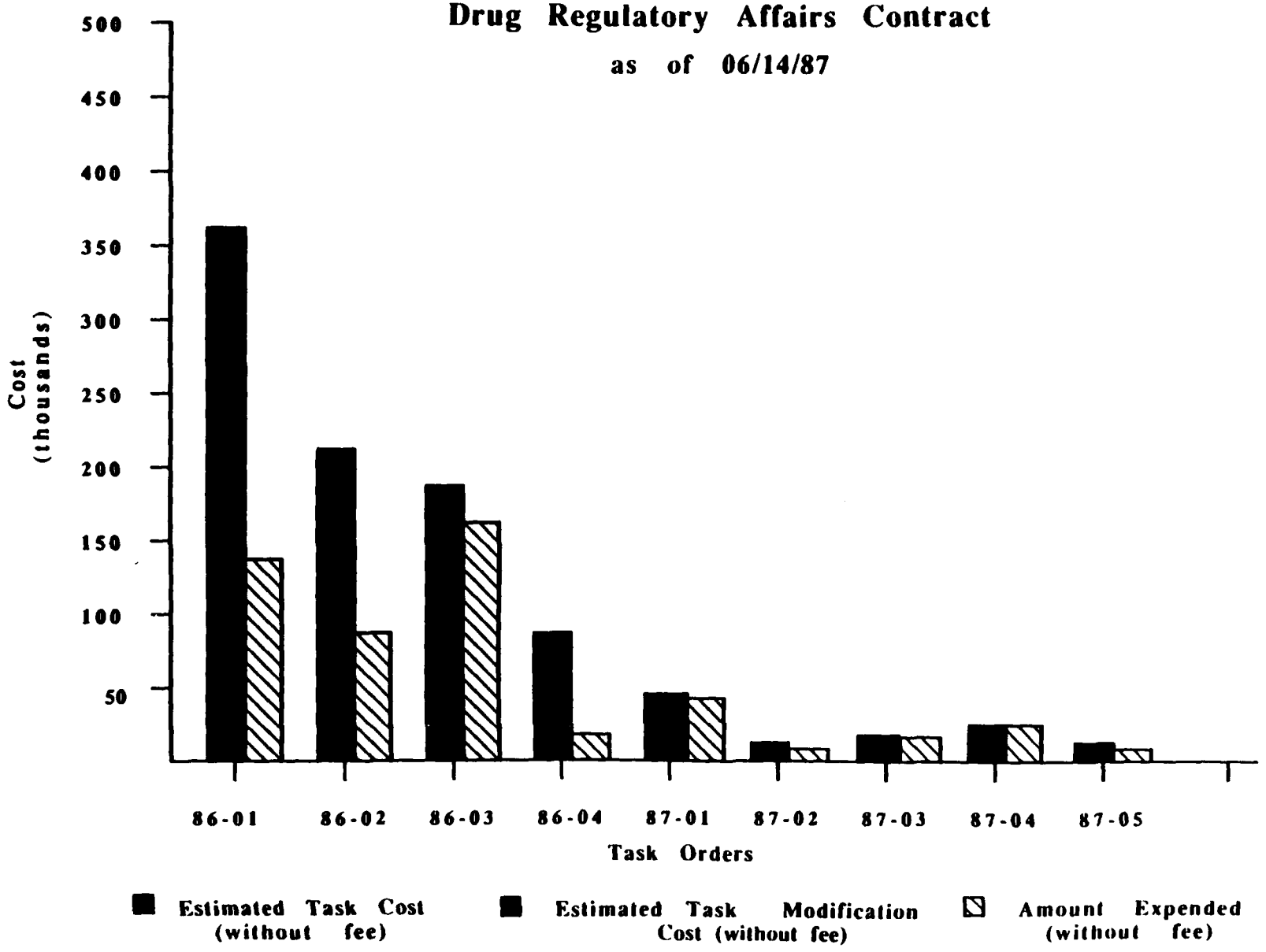
Task Order	Deliverable	Submission Date	Status of Task Order	Status of Subtask
87-01	Halofantrine		in progress	
	Task Progress Report	1/21/87		complete
	Task Progress Report	2/19/87		complete
	Draft Pre-NDA Report	3/23/87		complete
	Final Pre-NDA Report			
87-02	Acetylcholinesterase Literature Review		complete	
	Executive Summary	11/04/86		complete
	Draft Summary Section 6	12/10/86		complete
	Final Summary Section 6	2/09/87		complete
87-03	Atropine Pharmacokinetic Analysis		complete	
	Draft Report	1/04/87		complete
	Final Report	3/16/87		complete
87-04	Pyridostigmine Pharmacokinetic Analysis		in progress	
	Draft Report	3/27/87		gov't review
	Final Report			
87-05	Pyridostigmine-Acetylcholinesterase Statistical Study		in progress	
	Draft Report	6/26/87		gov't review
	Final Report			

AMR - PLANNED COST SCHEDULE

DATE TASK APPROVED BY CO	TASK NO.	DOLLAR AMOUNT APPROVED WITH FEE	TOTAL CUMULATIVE AMOUNT WITH FEE	START DATE	STOP DATE	DURATION
07/02/86	8601	375,973	375,973	06/02/86	06/01/88	24 months
07/08/86	8602	62,714	438,687	06/18/86	06/17/87	12 months
07/18/86	8603	180,343	619,030	07/01/86	05/01/87	10 months
08/26/86	8604	88,628	707,658	07/01/86	06/01/88	23 months
10/20/86	8701	59,887	767,545	10/28/86	03/31/87	5 months
11/04/86	8702	18,328	785,868	10/20/86	01/30/87	3 months
12/04/86	8703	28,496	814,364	10/27/86	02/28/87	4 months
12/04/86	8704	21,190	835,554	10/27/86	02/28/87	4 months
02/25/87	8704 (MOD 1)	4,823	840,377	10/27/86 (02/25/87)	04/30/87	2 months
03/26/87	8705	23,638	864,015	02/12/87	04/30/87	3 months
04/07/87	8602 (MOD 2)	172,711	1,036,726	02/11/87 (04/07/87)	12/31/87	9 months
05/29/87	8601 (MOD 1)	7,054	1,043,780	06/02/87	07/01/88	13 months
06/11/87	8603 (MOD 1)	23,812	1,067,592	07/01/87	09/30/87	3 months

( ) Effective Date of Modification

Estimated vs Expended



Financial Information[1]
DAMD17-86-C-6189
as of 6/14/87

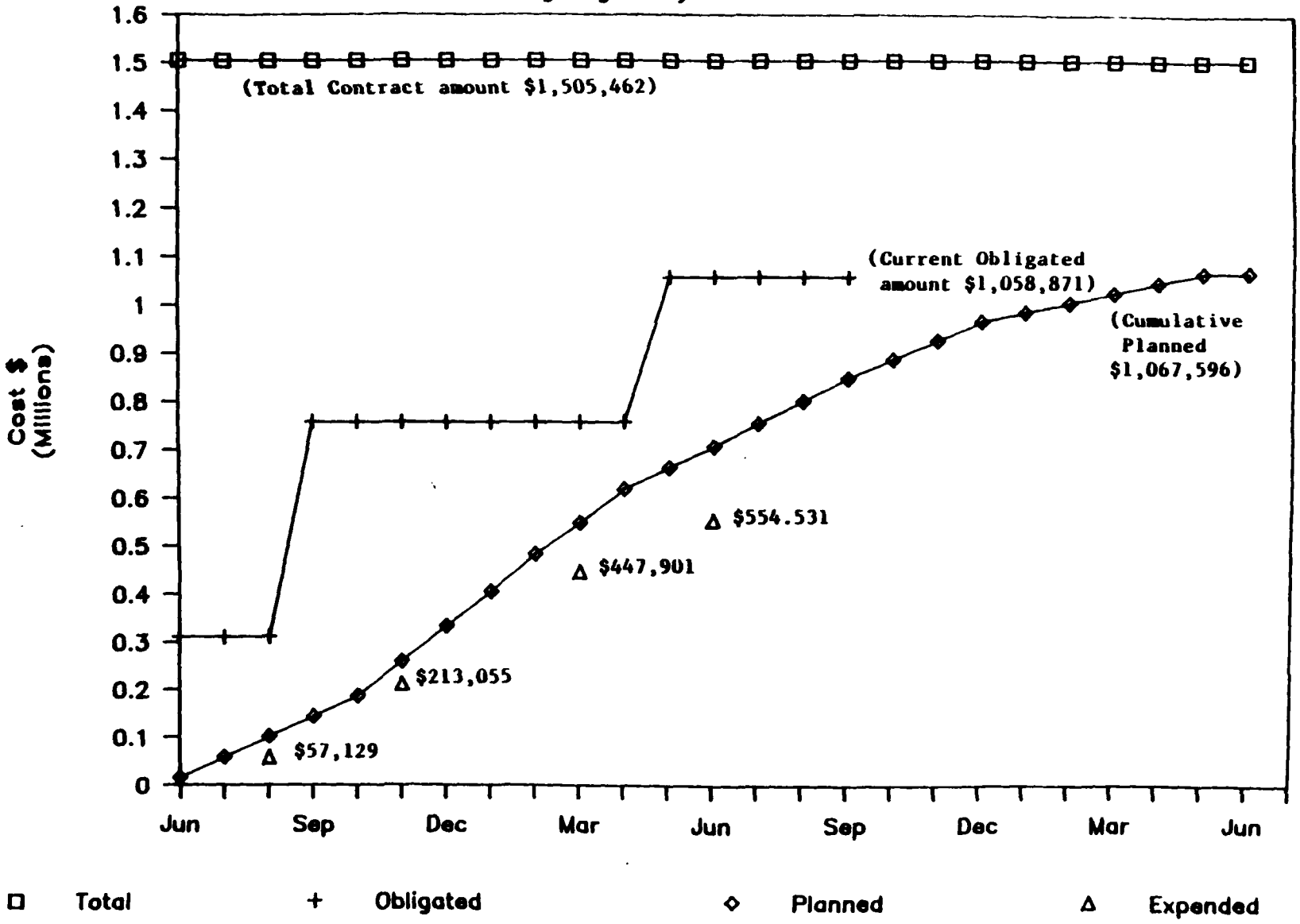
Task No.	Funds Negotiated	Cost Incurred	$ Expended (%)
8601	356,636	143,706	40.3
8602	220,021	81,486	37.0
8603	193,852	167,365	86.3
8604	81,310	23,965	29.5
8701	57,635	52,915	91.8
8702	16,815	15,822	94.1
8703	27,539	27,371	99.4
8704	24,168	24,327	100.7
8705	21,558	18,869	87.5
Total Contract Amount Negotiated	1,418,982		
Amount Expended through 6/14/87		555,826	
Percent of total contract amount negotiated expended through 6/14/87			39.2

([1]) These figures do not include fee.

The total number of manhours expended to date is 11,520.

Financial Analysis

Drug Regulatory Affairs Contract



5. Summary and Conclusion

Significant progress was made during the first year of the Drug Regulatory Affairs contract. A total of nine tasks and 12 subtasks were submitted to the contractor during this performance period. All tasks/subtasks were completed within the projected delivery schedule and cost estimate as described in respective Task Execution Plans. Remaining scheduled work is proceeding on schedule.

This technical progress was achieved through effective and timely interaction with the Contracting Officer's Representative, Dr. Paul Lish, and other members of the Pharmaceutical Systems Project Management Office. The contractor wishes to express appreciation for the excellent and cooperative professional relationship developed during this initial contract year.

6. Recommendations

An Annual Program Plan identifying the type of upcoming tasks and projected schedules would be of great value to the contractor and USAMMDA. This plan would facilitate better planning and administration of the task orders under this contract.

In addition to regulatory affairs support, EER would also like to provide technical and product management assistance to USAMMDA for all stages of the drug development process.

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