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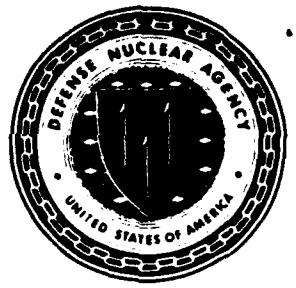

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Acute Radiation Sickness Amelioration Analysis

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13. ABSTRACT *(Maximum 200 words)*

Three tasks were conducted under the Acute Radiation Sickness Amelioration Analysis in support of the Defense Nuclear Agency (DNA) and NATO Army Armaments Group (NAAG) Project Group 29 (PG-29) on drugs for the prevention of radiation-induced nausea and vomiting: (1) documents were collected and entered into a data base, (2) data reviews and analyses were performed, and (3) PG-29 and Triservice meetings involving anti-emetic drug development were supported and documented.

Approximately 2000 documents were collected, with 1424 complete bibliographic citations entered into a WordPerfect 5.1 data base. Eight reviews and analyses addressing different aspects of the safety and efficacy of the candidate anti-emetic drugs ondansetron and granistron were prepared. Support was provided for seven international PG-29 meetings and two U.S. Triservice meetings in which the efforts of PG-29 were discussed. These tasks have enabled the DNA and PG-29 to make good progress toward the goal of recommending a serotonin type-3 (5-HT3) receptor antagonist anti-emetic drug for use in military personnel.

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SUMMARY

Serotonin type-3 (5-HT3) receptor antagonists were identified in the early to mid-1980s as a new class of anti-emetic drugs, with efficacy against radiation-induced emesis and no overt toxicity. In October 1989, Project Group 29 (PG-29) of the NATO Army Armaments Group (NAAG) was formed to evaluate 5-HT3 receptor antagonists for protection of military personnel against radiation-induced nausea and vomiting. Three tasks were conducted under the Acute Radiation Sickness Amelioration Analysis (Contract No. DNA 001-90-C-0111) to support PG-29 and the Defense Nuclear Agency (DNA) in the evaluation of 5-HT3 receptor antagonist anti-emetic drugs: (1) documents were collected and entered into a data base, (2) data reviews and analyses were performed, and (3) PG-29 and Triservice meetings involving anti-emetic drug development were supported and documented.

Approximately 2000 documents relevant to the development of the candidate anti-emetic drugs ondansetron (Zofran, Glaxo Pharmaceuticals) and granisetron (Kytril, SmithKline Beecham Pharmaceuticals) were collected. For 1424 of these documents, complete bibliographic citations were entered into a WordPerfect 5.1 data base for use by the DNA Technical Manager and the other members of PG-29. The collected documents included published articles from journals and newsletters, meeting abstracts, prepublications research data, and proprietary reports furnished by pharmaceutical manufacturers.

With the aid of the document collection, eight literature-based reviews and analyses were prepared in which the two candidate drugs were contrasted. Specifically addressed were: side effects in man and toxicity in animals, potential effects on thermoregulation, suggested doses for drug safety trials in volunteers, efficacy against radiation-induced emesis, effects on the cardiovascular system, drug activity and bioavailability, and potential drug-drug interactions.

Technical and administrative support was provided for seven international PG-29 meetings. Computer equipment was provided for real-time word processing and revision of documents such as the Terms of Reference, NATO Staff Requirement, Statement of Work, meeting minutes, and status reports. Additional support was provided to two Triservice meetings held in the United States by the U.S. Army Nuclear and Chemical Agency (USANCA) for Department of Defense (DoD) staffing of PG-29 documents. An exhibit depicting the timeline for the DNA anti-emetic drug development effort was constructed and displayed at the 2nd and 3rd Annual Radiation Risk/Safety Program Technology Transfer Meetings.

The tasks conducted under the Acute Radiation Sickness Amelioration Analysis has enabled PG-29 to meet its interim milestones and make good progress toward its goal of making a final recommendation to the NAAG in mid-1996.

PREFACE

The reviews and analyses conducted under the Acute Radiation Sickness Amelioration Analysis were performed with the aid of published and unpublished documents. No studies were performed with laboratory animals or human subjects.

The authors wish to express sincere thanks to the following two individuals for conceiving and guiding the Acute Radiation Sickness Amelioration Analysis:

Dr. Robert W. Young, Chairman and U.S. Scientific Representative to NATO Army Armaments Group Project Group 29, and Manager, Defense Nuclear Agency Radiation Risk/Safety Program

Mr. Robert Kehlet, Nuclear Research Program Manager, Defense Nuclear Agency Radiation Risk/Safety Program

Appreciation is also extended to the following individuals and groups for their efforts in providing timely information and data in support of the Acute Radiation Sickness Amelioration Analysis tasks:

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STATEMENT OF THE PROBLEM

1.1 MILITARY NEED FOR AN ANTI-EMETIC DRUG.

Nausea and vomiting are among the first symptoms to occur in acute radiation sickness (Young, 1987; Harding, 1988). The Defense Nuclear Agency (DNA) Human Response Program has identified nausea and vomiting as the primary impediment to sustained military operations capability after exposure to ionizing radiation at free-in-air doses up to 1000 Gray (Gy). For certain military tasks, just one episode of vomiting can have a significant negative impact on performance. A drug that is capable of preventing all radiation-induced emesis is therefore desired by the Department of Defense (DoD) as a self-administered field item for use in Servicemembers (Academy of Health Sciences, 1991). Because military personnel are currently outfitted with multiple autoinjectors for postexposure treatment of nerve agent toxicity, the DoD has requested that any anti-emetic drug intended for self-administration be fielded as an easy-to-use oral formulation.

Established anti-emetic drugs from several drug classes are able to diminish radiation-induced emesis; however, the protection they provide is not complete (Young, 1986). Furthermore, all of these drugs produce undesirable side effects that can affect military performance. These include sedation and drowsiness, and in some instances, altered perception or a characteristic pattern of behavioral disturbances (Bloom, 1990; Brunton, 1990).

Selection of an appropriate anti-emetic drug for use in military personnel requires the efforts of individuals who have a comprehensive understanding of drug actions--both desirable actions such as anti-emetic efficacy and undesirable actions such as side effects, delayed toxicity, or toxic interactions with other drugs or substances. Through the Acute Radiation Sickness Amelioration Analysis, the DNA gained access to a team of scientists with extensive knowledge of pharmacological principles.

1.2 U.S. MILITARY DRUG DEVELOPMENT REQUIREMENTS.

Drugs developed for use in U.S. military personnel must meet the requirements for approval set forth by the U.S. Food and Drug Administration (FDA) and additional requirements designated by the Services' Surgeons General. To meet the requirements of the FDA, studies equivalent to those conducted by commercial pharmaceutical manufacturers are needed. One important difference, however, is the conduct of efficacy studies. Since it is not ethical to expose healthy subjects representative of military populations to toxic doses of ionizing radiation or chemical warfare agents, demonstration of efficacy for an intended use or indication can be hampered.

There are presently no standardized military drug development requirements within the U.S. DoD or its three Services. It is the responsibility of the military drug development proponent to identify the military-specific issues that need to be addressed and to present the case that consideration has been given to all conceivable issues of military concern. After review of a proponent's final report, the

Surgeons General indicate whether sufficient information has been collected, and if not, which additional studies should be undertaken.

To increase the chances that its anti-emetic drug development effort will be judged acceptable by the FDA and the Services' Surgeons General, the DNA sought additional expertise in military drug development. The Acute Radiation Sickness Amelioration Analysis provided the DNA with scientists who had previously assisted the U.S. Army in research and development of drugs that protect Servicemembers against chemical warfare agents.

1.3 NATO PROJECT GROUP REPORTING REQUIREMENTS.

NATO Projects Groups are short-lived cooperative ventures that are organized for completion of a specific, well-defined task. NATO Army Armaments Group (NAAG) Project Group 29 (PG-29) on drugs for the prevention of radiation-induced nausea and vomiting was given a 5-year charter to develop a recommendation regarding selection of a serotonin type-3 (5-HT3) receptor antagonist anti-emetic drug for use in military personnel.

To conform with NAAG regulations, a Project Group must draft and obtain national approvals for the following documents: (1) the Terms of Reference, which outlines the policies and procedures of the Project Group; (2) a NATO Staff Requirement, which lists the requirements for the item that is to be jointly developed, and (3) a Statement of Work, which explicitly states which nations will be responsible for undertaking each portion of the cooperative development effort. Additional NATO reporting requirements include official minutes for each meeting of the Project Group, semiannual progress reports for presentation to the NAAG by the Project Group Chairman, and a Final Report communicating conclusions and recommendations at the end of the Project Group's charter period.

To meet the administrative demands imposed by membership in a NATO Project Group, the DNA sought additional meeting support and document processing capability over that provided by a NAAG-assigned Project Group Secretary. The Acute Radiation Sickness Amelioration Analysis provided PG-29 with an expanded scientific, editorial, administrative, and clerical staff for assistance in meeting NATO reporting requirements.

SECTION 2

BACKGROUND

2.1 DISCOVERY OF A NEW CLASS OF ANTI-EMETIC DRUGS.

A new class of compounds synthesized in the early to mid-1980s was found to be highly selective at antagonizing the actions of the neurotransmitter serotonin at serotonin type-3 (5-HT3) receptors (Kilpatrick *et al.*, 1990). Included in this class were: MDL 7222 (Lily), ICS 205-930 (later named tropisetron, Sandoz), zacopride (A. H. Robbins), GR 38032 (later named ondansetron, Glaxo), and BRL 43694 (later named granisetron, Beecham). The similar actions of these compounds could be attributed to like chemical structures in some instances, but not in others.

Among the spectrum of pharmacological actions attributed to 5-HT3 receptor antagonists was prevention of cytotoxic drug- and radiation-induced emesis. Studies conducted in ferrets and dogs (species that display vomiting) demonstrated that some of the new compounds were extremely effective at preventing vomiting and retching when administered as a prophylaxis 5-45 minutes prior to a radiation exposure. Of note, it was found that metoclopramide, the most efficacious of the existing anti-emetic drugs, also acted as an antagonist at 5-HT3 receptors. Unlike the newer, more specific 5-HT3 antagonists listed above, however, metoclopramide also acts as an antagonist at dopamine type-2 receptors. It is known that the dopamine-blocking actions of metoclopramide are responsible for the undesirable side effects produced by this drug and a number of other less-effective anti-emetic drugs.

2.2 COMMERCIAL DRUG DEVELOPMENT EFFORTS.

2.2.1 Pre-1990 Efforts.

Before the start of the Acute Radiation Sickness Amelioration Analysis in July 1990, clinical trials had already been conducted by pharmaceutical companies with three of the new 5-HT3 antagonist compounds--ondansetron, granisetron, and tropisetron. These drugs had been administered to healthy volunteers for determination of safety and tolerability, and to cancer patients undergoing cytotoxic chemotherapy or radiotherapy for determination of anti-emetic efficacy. Commercial development of ondansetron and granisetron was proceeding at a rapid rate, while development of tropisetron appeared to lag behind. The trade name of Zofran was adopted for ondansetron; the trade name Kytril was adopted for granisetron.

The first approval for ondansetron was obtained in the United Kingdom. Both intravenous and oral ondansetron formulations could be used against "cytotoxic therapy-induced emesis." Total body irradiation (TBI) and radiotherapy are included in the definition of cytotoxic therapy in the United Kingdom.

2.2.2 Post-1990 Efforts.

Worldwide development of the three anti-emetic drugs, ondansetron, granisetron, and tropisetron, continued during the course of the Acute

Radiation Sickness Amelioration Analysis. Granisetron was approved for the first time in France for use as an intravenous drug against cytotoxic chemotherapy drug-induced emesis. This approval did not extend to TBI- or radiotherapy-induced emesis.

Of the three drugs undergoing development, only ondansetron and granisetron qualified as candidate drugs for consideration by PG-29, based on the following definition for candidate drug appearing in the PG-29 Statement of Work (NATO Army Armaments Group, 1992):

> "A Serotonin-Type 3 (5-hydroxytryptamine-receptor subtype 3 or 5H3) receptor antagonist anti-emetic drug that as of January 1992 (1) has been approved for civilian use as an anti-emetic in one or more PG-29 member nations; and (2) has published data showing efficacy in humans against radiation-induced nausea and vomiting."

Table 2-1 indicates the approval status of ondansetron and granisetron in the five PG-29 nations as of May 1993. At the present time, neither ondansetron not granisetron have yet been approved for the critical indication of radiation-induced emesis in the United States.

Table 2-1. Approval status of ondansetron and granisetron in the five PG-29 nations.

Nation	Ondansetron	Granisetron
Canada	Intravenous and oral formulations approved for cytotoxic chemotherapy drug-induced emesis	Not approved as of May 1993
France	Intravenous and oral formulations approved for cytotoxic chemotherapy drug-induced emesis	Intravenous and oral formulations approved for cytotoxic chemotherapy drug-induced emesis
Spain	Intravenous and oral formulations approved for cytotoxic chemotherapy drug and radiation-induced emesis	Intravenous formulation approved for cytotoxic chemotherapy drug- and radiation-induced emesis
United Kingdom	Intravenous and oral formulations approved for cytotoxic chemotherapy drug- and radiation-induced emesis	Intravenous formulation approved for cytotoxic chemotherapy drug- and radiation-induced emesis
United States	Intravenous and oral formulations approved for cytotoxic chemotherapy drug-induced emesis	Not approved as of May 1993

2.3 LEVERAGING OF CRITICAL DATA.

A key feature of the DNA Radiation Risk/Safety Program anti-emetic drug development effort is that it relies heavily on non-DoD sources for collection of critical data. By leveraging information from the commercial drug manufacturers and other nations interested in an anti-emetic drug for military applications, the high cost of developing a new drug has been significantly reduced.

2.3.1 Formation of PG-29.

PG-29 was formed in October 1989 as an international cooperative effort to address military-specific issues pertaining to development of a 5-HT3 receptor antagonist anti-emetic drug. Its final membership consists of Scientific and Military Representatives from Canada, France, Spain, the United Kingdom, and the United States. Some PG-29 members assume the role of both Scientific and Military Representative. The U.S. Scientific Representative to PG-29 was elected as the Project Group's Chairman.

Since its formation, PG-29 has met at least twice a year at various locations within its five PG-29 member nations and at NATO Headquarters in Brussels, Belgium. Although a NATO secretary was originally assigned to PG-29 by the NAAG, performed duties were limited by budget constraints and the position was eliminated in 1992.

The initial task of PG-29 was to define the military concept of use and all required characteristics for an anti-emetic drug. Subsequent to the five-nation agreement regarding what was to be developed (specified in the NATO Staff Requirement), the Project Group's next task was to decide how the anti-emetic drug would be developed.

2.3.2 Development of the PG-29 Statement of Work.

The PG-29 Statement of Work reflects the combined efforts of the five member nations at deciding which tasks are necessary for selection of a specific anti-emetic drug for military use. Each nation had the opportunity to request specific studies deemed necessary for the drug selection process. The specific tasks included in the PG-29 Statement of Work are those that were requested by two or more member nations. (Studies desired by the United States, but not incorporated into the PG-29 Statement of Work, can still be conducted by the U.S. DoD.)

Once the necessary drug development tasks were agreed upon, the tasks were assigned to the member nations. In general, each nation retained responsibility for planning, financing, and monitoring performance on the tasks assigned to it. However, the Statement of Work states that the results of all tasks conducted in support of the PG-29 Statement of Work must be shared with the five PG-29 nations, and provided in an agreed-upon format. The data format specified in the PG-29 Statement of Work reflects the requirements of the FDA.

2.3.3 Interactions with Pharmaceutical Companies.

To limit the scope of the DNA and PG-29 drug development efforts to only those tasks that are specific to the military concept of anti-emetic drug use, lines of communication were established with the manufacturers of ondansetron and granisetron. Glaxo and SmithKline

Beecham have provided proprietary reports containing highly detailed descriptions of safety and efficacy studies, and selected portions of applications submitted to the FDA and European drug regulatory agencies. Representatives from these pharmaceutical companies have also provided information on planned and ongoing studies, and on current regulatory status within each PG-29 nation. The pharmaceutical companies have been invited to make presentations at PG-29 meetings and to provide periodic updates.

Both pharmaceutical manufacturers are assisting PG-29 in performance of tasks described in the PG-29 Statement of Work. The companies are providing investigators within the member nations with necessary quantities of investigational drug supplies, and are permitting cross-referencing of on-file pharmaceutical company data for completion of Investigational New Drug applications.

PG-29 has encouraged the pharmaceutical manufactu to conduct efficacy studies with oral anti-emetic drug formu ons in bone-marrow-transplant patients who receive total-body irradiation (TBI) without concomitant cytotoxic drugs. Such study conditions have been judged by PG-29 to be the most representative of a human battlefield radiation exposure. PG-29 has also encouraged the pharmaceutical manufacturers to seek specific regulatory agency approvals for the indication of radiation-induced emesis.

SECTION 3

APPROACH

3.1 CONSTRUCTION OF DATA BASE.

Documents relevant to the development of a 5-HT3 receptor antagonist anti-emetic drug were identified through electronic data bases that included the National Library of Medicine's MEDLINE data base and the EMBASE and BIOSIS PREVIEWS data bases (accessed through DIALOG Information Services). Published journal articles were retrieved from the National Institutes of Health Medical Library in Bethesda, Maryland, and other medical libraries, as necessary. After determining that important and timely information on developments within the pharmaceutical industry, the FDA, and the European drug regulatory agencies are routinely reported in Scrip World Pharmaceutical News, a subscription to this biweekly newsletter was purchased for the Acute Radiation Sickness Amelioration Analysis. Additional sources of documents included the proceedings of professional meetings attended by PG-29 members, and satellite symposia sponsored by the manufacturers of 5-HT3 receptor antagonist drugs. A unique document identification number was assigned to each document intended for electronic data base entry. Hardcopies of these documents were filed by identification number and stored at the Science Applications International Corporation Life Sciences Division Office in Joppa, Maryland.

Proprietary reports and regulatory agency documentation on ondansetron and granisetron were provided to PG-29 and the Acute Radiation Sickness Amelioration Analysis staff by Glaxo and SmithKline Beecham, respectively. These documents were stored separately in a locked cabinet in the Joppa, Maryland, office. Only a limited number of staff members had access to these documents; however, all staff members, consultants, and subcontractor personnel contributing to the Acute Radiation Sickness Amelioration Analysis were required to sign non-disclosure of proprietary information agreements.

An electronic WordPerfect 5.1 reference data base, which includes complete bibliographic citations for each entered record, was created for document tracking and for feed-in into a more extensive electronic anti-emetic drug data base. To enhance the utility of this system, a macro was constructed for interconversion of numerical and alphabetical record listings. Updated listings of all documents entered into the WordPerfect data base, and separate listings of newly entered documents were prepared for distribution to the members of PG-29 at each PG-29 meeting.

It was originally planned to construct an electronic anti-emetic drug data base in the INGRES Relational Database Management System on a VAX network resident at Los Alamos National Library. This plan was abandoned after it became known that the DNA Technical Manager did not have access to this system. In conjunction with the DNA, plans were made to construct an alternate data base in Oracle that would be housed on a 386 IBM-compatible Personal Computer and eventually transferred to the DNA and the members of PG-29. Data entry forms based on WordPerfect document files were designed and constructed along with macros to convert data files into a format readable by Oracle. Data tables were constructed in Oracle. Efforts directed

toward completion of the drug data base were halted at the direction of the DNA when it became apparent that the data needs of the DNA and PG-29 were changing in response to new developments in the field of 5-HT3 receptor antagonists. To keep pace with the rapid advances in this field, the size of the document collection and electronic WordPerfect data base was expanded to include many more documents than the original estimate of 300-500.

3.2 ANALYTICAL PROCEDURES.

To conduct analyses in support of the DNA and PG-29, a team of scientists that included pharmacologists, a biochemist, a physiologist, and a systems analyst was employed. For each requested analysis, an approach to identifying and presenting relevant data was developed so that conclusions independent of those drawn by the Acute Radiation Sickness Amelioration Analysis staff could be drawn by the DNA and the members of PG-29. The analytical procedures developed for each review and analysis were aimed toward providing directly comparable information for the two candidate drugs. Whenever possible, data and results were presented in tabular or graphic form. In all instances, employed analytical approaches were described in accompanying text.

Much of the available data on the two candidate drugs derived from preclinical studies in animal models displaying 5-HT3 receptor-mediated activity profiles that are different from those of humans, or from clinical trials employing non-oral-drug formulations in seriously ill patients. It was therefore necessary to apply pharmacological principles and available information on species-specific, route-specific, and illness-specific differences to extrapolate from available data to predict potential effects of an orally administered anti-emetic drug formulation in healthy military personnel.

3.3 SUPPORT AND DOCUMENTATION OF MEETINGS.

In preparation for each PG-29 meeting, Acute Radiation Sickness Amelioration Analysis scientists met or engaged in a teleconference with the DNA Technical Manager, who is the U.S. Scientific Representative and Chairman of PG-29, to discuss the meeting agenda and the results of any analyses intended for presentation to PG-29. To provide accurate and complete documentation of meeting discussions and additional technical or administrative support as needed, two biomedical scientists attended each PG-29 meeting. In addition to note-taking and on-site word processing, the scientists were able to provide overnight analyses of newly presented data.

Finalized versions of PG-29 documents were usually prepared after the conclusion of a meeting, so that they could be subjected to careful editing and formatting in accordance with NATO or other requirements. The first document to be prepared for dissemination to the DNA or PG-29 after the conclusion of a meeting was usually a complete listing of the action items.

3.4 PREPARATION OF CONTROLLED-DISTRIBUTION DOCUMENTS.

To ensure that newly generated documents that contained proprietary information or results based on proprietary information were not made available to unauthorized individuals, several precautionary measures

were employed. All copies of reviews and analyses, records of discussions, and interim status reports (including draft versions and copies intended for storage) were numbered. A listing of the authorized recipients for a given document, and the copy number assigned to each of these recipients appeared just after the cover page of each controlled-distribution document. In addition, each page of every controlled-distribution document carried the marking "COMMERCIAL-IN-CONFIDENCE" at the top and bottom margins. Because prepared interim status reports contained information that could serve as the basis for a future procurement decision, a comprehensive "eyes only" warning was printed on the bottom of each page. The precautions taken with these documents were judged to be appropriate by the DNA and the members of PG-29.

SECTION 4

ACCOMPLISHMENTS

4.1 DOCUMENTS COLLECTED AND ENTERED INTO A DATA BASE.

Approximately 2000 documents relevant to the development of an anti-emetic drug have been collected. The majority of these documents pertain to the clinical safety, preclinical toxicity, anti-emetic efficacy, pharmacokinetics, possible drug interactions, formulation characteristics, and mechanisms of action of ondansetron and granisetron. The remainder of the documents address issues such as FDA regulatory requirements, methodology for determining anti-emetic efficacy, use of ondansetron and granisetron for indications other than emesis, the development status of candidate and non-candidate 5-HT3 receptor antagonists, and financial and legal matters relating to drug cost and the manufacturers' ability to provide the drugs.

Complete bibliographic citations for 1424 of the collected documents have been entered into a WordPerfect 5.1 reference data base. Because the development of 5-HT3 antagonists proceeded much more rapidly than originally anticipated, the number of documents collected and entered into this data base in support of the Acute Radiation Sickness Amelioration Analysis is much greater than the initial estimate of 300-500. The reason for the expansion is that 5-HT3 receptor antagonists have shown promise for a number of medical indications beyond the first-proposed anti-emetic indications. The potential financial gains associated with additional indications such as postoperative emesis, irritable bowel syndrome, migraine, anxiety, schizophrenia, and age-associated memory loss have prompted a large number of pharmaceutical manufacturers to enter the field. Data collected from studies conducted in support of these additional indications have provided important insight into the potential impacts of ondansetron and granisetron on military performance.

The WordPerfect reference data base has been used on numerous occasions to identify relevant documents for inclusion in data reviews and analyses. In addition, printouts from the reference data base have been used by the members of PG-29 as a tool to keep abreast of technical and regulatory developments in the field of 5-HT3 receptor antagonists. Hardcopies of collected documents have been furnished to the members of PG-29 as requested, or in the case of extremely important new information, automatically.

4.2 REVIEWS AND ANALYSES CONDUCTED FOR PG-29 AND THE DNA.

Eight reviews and analyses were conducted at the request of PG-29 or the DNA. Each addressed a topic that was of concern or interest at the time of the request. The overall aim of these reviews and analyses was to determine whether one or both candidate drugs should be dropped from consideration for use as an anti-emetic in military personnel. In some cases, these analyses were also used to determine research directions for PG-29-sponsored studies. In subsequent sections, the purpose and characteristics of each review and analysis are described. Because the analyses are heavily based on proprietary information that is specific for two commercial drug products in

direct worldwide competition, detailed results and conclusions are not discussed in the present report.

4.2.1 Toxicity of Ondansetron and Granisetron: A Comparative Analysis.

The purpose of this analysis was to determine whether one or both candidate drugs demonstrate a human toxicity profile that should preclude its use as an anti-emetic drug in military personnel. The analysis was requested by PG-29 during the 3rd PG-29 Meeting in July 1990.

All available documents, including proprietary reports furnished by the pharmaceutical companies, were reviewed for clinical data on adverse events ranging from innocuous side effects to life-threatening reactions. Tables listing the incidence of specific and total adverse events were prepared for each drug, with consideration given to the route of drug administration. Separate tables were prepared for healthy volunteers, for cancer patients receiving cytotoxic chemotherapy, and for cancer patients receiving total-body irradiation (TBI) or localized radiotherapy. Data were presented both by individual study and as a pooled incidence rate for each adverse event. A summary table was prepared that included the pooled results for each drug in each study population.

A briefing of the analysis was presented at the 4th PG-29 Meeting in October 1990. The results of the analysis suggested that neither drug should be dropped from further evaluation. However, a more comprehensive analysis, which addresses preclinical toxicology and the dose-response characteristics of each effect, was requested by PG-29.

4.2.2 Comparative Analysis of the Preclinical Toxicology and Clinical Safety of Ondansetron and Granisetron.

The purpose of this comprehensive analysis was to determine whether one candidate drug has a less favorable toxicity profile than the other and whether any special precautions are needed for the conduct of PG-29-sponsored trials in volunteers. The analysis was requested by PG-29 at the 4th PG-29 Meeting in October 1990.

Data for the analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers. Preclinical data on the various aspects of acute, subacute, and chronic drug toxicity were presented in tables or on dose-response lines. Preclinical and clinical data on the gastrointestinal effects of the two candidate drugs and other 5-HT3 antagonists were presented in text form. Preclinical and clinical data on the behavioral effects of the two candidate drugs and other 5-HT3 antagonists were presented in tabular form. Pooled incidence data on adverse events in healthy volunteers, chemotherapy patients, and TBI or radiotherapy patients were presented in tabular form. Consideration was given to drug-specific and species-specific differences in absorption, distribution, metabolism, and elimination (ADME) so that observed effects in animals and humans could be compared. A summary dose-response line was provided, which indicated the range of doses (expressed in mg/kg) at which anti-emesis and various toxicological and behavioral effects could be observed across

all species examined. Superimposed on the dose-response line was the recommended clinical dose for anti-emesis. In all instances, data on the two candidate drugs were presented side by side to facilitate comparison.

A briefing of the analysis was presented at the 5th PG-29 Meeting in May 1991. The results of the analysis suggested that neither drug should be dropped from further evaluation. It was suggested by PG-29 that an update of the toxicology and safety analysis might be necessary in the future as more data become available for consideration.

4.2.3 Possible Effects of 5-HT3 Receptor Antagonist Anti-emetic Drugs on Thermoregulation.

The purpose of this analysis was to determine whether there is reason to suspect that 5-HT3 receptor antagonists such as ondansetron or granisetron might produce adverse effects on thermoregulation, and how to best evaluate potential effects on thermoregulation in an animal model. The analysis was requested by PG-29 at the 4th PG-29 Meeting in October 1990.

Data for the review and analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers. The review and analysis was conducted in two phases, with a separate series of questions addressed in each (see Table 4-1). Findings pertaining to the questions were provided and their implications were discussed. An annotated bibliography of all reviewed documents was prepared.

A briefing of the analysis was presented at the 5th PG-29 Meeting in May 1991. The results of the analysis suggested that no interpretable information pertaining to the effects of ondansetron or granisetron in humans could be gained from conducting studies of thermoregulation in an animal model.

Table 4-1. Questions addressed in each phase of the thermoregulation analysis.

Questions addressed in Phase I:

(1) Why is there concern regarding 5-HT3 receptor antagonist anti-emetic drugs and thermoregulation?

(2) How have serotonergic mechanisms been implicated in thermoregulation?

(3) What are the anatomical sites associated with thermoregulation?

(4) Are there data suggesting a direct relationship between 5-HT3 receptors and thermoregulatory mechanisms?

(5) Do any of the serotonergic ligands known to affect thermoregulation cross-react with 5-HT3 receptors?

(6) Do ondansetron or granisetron cross-react with receptors known to be involved in thermoregulation?

(7) Are there 5-HT3 receptors in the brain regions associated with thermoregulation?

Questions addressed in Phase II:

(1) What animal models are most suitable for studies of thermoregulation?

(2) What animal models are most similar to humans with respect to 5-HT3 receptor function and localization, and disposition of ondansetron and granisetron?

(3) What are the measurements made in thermoregulation studies and how are they made?

4.2.4 Selection of Drug Doses for PG-29-Sponsored Studies.

The purpose of this analysis was to recommend which oral doses of ondansetron and granisetron should be considered for use in PG-29-sponsored human studies. The analysis was requested by PG-29 at the 5th PG-29-Meeting in May 1991. At the time the analysis was requested, limited data were available on the effects of these drugs in TBI or radiotherapy patients, and in most instances the data were for the intravenous drug formulation.

Data for the analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers, and unpublished research data. To conduct the analysis, dose-response curves for anti-emetic efficacy in various studies were constructed, pooled, and contrasted. For each drug, comparisons were made of the following composite dose-response

profiles: (1) human versus ferret, (2) intravenous versus oral, and (3) radiation versus cisplatin-containing chemotherapy. Two types of dose-response curves were constructed in each instance--one in which the y-axis was percent number of control emetic episodes, the other in which the y-axis was percent of number of animals or patients that experienced vomiting. For studies conducted in humans, a third dose-response curve was constructed in which the y-axis was percent number of patients that experienced nausea. Based on the composite anti-emetic profiles, recommended oral dose ranges were selected. Following selection of dose range, dosing interval-response curves were constructed and pooled for studies conducted in humans at different drug doses. Based on the combined dose-response and dosing interval-response data, recommended dosing regimens were selected.

A briefing of the analysis was presented at the 6th PG-29 Meeting in September 1991. For one of the candidate drugs, the results of the analysis suggested an oral dose that was lower than that originally anticipated. Subsequent to and independent of the analysis conducted for PG-29, the recommended daily dose for this drug was decreased by the manufacturer for certain indications. Final selection of drug doses for PG-29-sponsored human studies occurred at the 8th PG-29 Meeting in October 1992. Selected dosing regimens were based on new data and information provided by the pharmaceutical manufacturers.

4.2.5 Efficacy of Candidate Drugs against Radiation-Induced Emesis.

The purpose of this review was to organize all available data on the efficacy of the two candidate drugs against radiation-induced emesis so that the overall efficacy of each drug could be determined and compared. The review was requested by PG-29 at the 7th PG-29 meeting in June 1992.

Data for the analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers, and unpublished or preliminary research data provided by the pharmaceutical manufacturers during oral presentations. Two types of tables were prepared for each drug--summary tables suitable for use in briefings and presentations, and comprehensive tables designed for critical analysis of each efficacy study. Consideration was given to whether additional drugs such as emesis-producing chemotherapy agents were employed as part of the study protocol. Included in all tables were: total radiation dose, number of radiation fractions administered over time, radiation dose rate, anatomic site of the administered radiation, dosing regimen for ondansetron or granisetron, patient sample size, and percent of patients experiencing no vomiting on given study days or over the course of an entire study. The comprehensive tables included additional details on study design, patient demographics, delivered radiation, and anti-emetic drug administration. The comprehensive tables also included appendixes indicating percent of patients experiencing no nausea and percent of patients experiencing specific adverse events.

A briefing of the review was presented at the 8th PG-29 Meeting in October 1992. The results of the review were used by PG-29 to determine which types of additional efficacy studies are needed before a final recommendation can be made on each candidate drug.

4.2.6 Review and Analysis of the Cardiovascular Effects of 5-HT3 Receptor Antagonists.

The purpose of this review and analysis was to determine whether specific 5-HT3 antagonist anti-emetic drugs or the whole class of 5-HT3 receptor antagonists are cardiotoxic. The analysis was requested by the DNA in April 1993 for presentation at the 9th PG-29 Meeting in June 1993. The request was based on concerns raised by FDA toxicologists during a meeting of the Gastrointestinal Drug Advisory Committee (U.S. Food and Drug Administration, 1993; Scrip World Pharmaceutical News, 1993) and by published reports on adverse cardiovascular events in cancer patients receiving ondansetron (Ballard *et al.*, 1992; Coates *et al.*, 1992).

Data for the analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers. Considered were cardiovascular effects in different animal models, and adverse cardiovascular events in volunteers and various patient populations. Because the data on cardiovascular effects were extensive, the decision was made to limit the scope of the effort to a comprehensive data review.

Data on the overall incidence of cardiovascular events and on specific effects or events were presented in tabular form for ondansetron, granisetron, and other 5-HT3 receptor antagonists. Included in each table were: 5-HT3 receptor antagonist dosing information, the health and medication status of the study population, and effect or event incidence in placebo, comparator drug- and/or 5-HT3 receptor-antagonist-treated subject populations.

A briefing of the review was presented at the 9th PG-29 Meeting in June 1993. Because relevant cardiovascular data would soon be available from PG-29-sponsored studies in healthy volunteers, PG-29 requested that no additional analysis take place without inclusion of the new data.

4.2.7 Parameters of 5-HT3 Receptor Antagonist Activity and Bioavailability.

The purpose of this review was to assemble all available data on the effective dose ranges for various drug actions, bioavailability of non-intravenous formulations, times to peak plasma drug levels after non-intravenous administration, and durations of drug action. Only ondansetron and granisetron were considered. The review serves as a reference guide for critical evaluation of data derived from studies conducted under different conditions. The review was requested by the DNA in March 1991.

Data for the review were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers. For each parameter considered in the review, information on both drugs, given in the same species via the same route, was presented side by side. The review was presented to the DNA in April 1991.

4.2.8 Survey of 5-HT3 Receptor Antagonist Interactions with Militarily Relevant and Non-Militarily Relevant Drugs.

The purpose of this review was to assemble available data on the potential interactions between 5-HT3 receptor antagonists such as ondansetron and granisetron and other drugs, with special consideration given to drugs of military relevance (i.e., chemical and biological warfare pretreatment and treatment drugs, emergency medical medications, and substances or drugs likely to be on board in military populations). Depending on the severity and likelihood of an identified adverse interaction, a decision could be made by the DNA to drop one or both candidate drugs from further consideration or to recommend a change in DoD doctrine. The review was requested by the DNA in March 1991.

Data for the analysis were obtained from published and unpublished documents, including proprietary reports furnished by the pharmaceutical manufacturers. Four data tables that included the results of individual studies were prepared: (1) Effect of 5-HT3 Receptor Antagonists on the Efficacy, Toxicity, and Disposition of Militarily Relevant Drugs, (2) Effect of Militarily Relevant Drugs on the Efficacy, Toxicity, and Disposition of 5-HT3 Receptor Antagonists, (3) Effect of 5-HT3 Receptor Antagonists on the Efficacy, Toxicity, and Disposition of Non-Militarily Relevant Drugs, and (4) Effect of Non-Militarily Relevant Drugs on the Efficacy, Toxicity, and Disposition of 5-HT3 Receptor Antagonists. Included in the tables were route and dose range for both drugs, species, parameter studied, and a qualitative statement of the observed effect.

A preliminary version of the review was presented to the DNA in May 1991. Subsequent to that time, an official listing of the militarily relevant drugs and substances that should be considered during military drug development efforts was prepared by the Academy of the Health Sciences. An update of the review was completed in July 1993.

4.3 MEETINGS SUPPORTED.

4.3.1 PG-29 Meetings.

Seven PG-29 meetings were supported by the Acute Radiation Sickness Amelioration Analysis. Notetaking and on-site computer support provided for accurate capture of meeting discussions and real-time processing and editing of PG-29 documents. A listing of all PG-29 meetings held to date, with an indication of those supported by the Analysis, is provided in Table 4-2. Documents that were prepared during or subsequent to PG-29 meetings are described in the sections that follow.

4.3.1.1 Minutes and Records of Discussions. For each PG-29 meeting supported, a draft version of meeting minutes was prepared. The minutes conformed to NATO-specified format and omitted proprietary information not suitable for public dissemination. Included as part of the minutes were: the date and location of the meeting, a listing of all attendees, any changes made to the draft meeting agenda, any changes made to the PG-29 Terms of Reference, all decisions reached during the meeting, action items resulting from the meeting, and plans for future meetings. At the request of the DNA, the draft meeting

Table 4-2. PG-29 meetings held to date.

Meeting	Location	Date	Supported by Acute Radiation Sickness Amelioration Analysis
1st	NATO Headquarters Brussels, Belgium	19 October 1989	No
2nd	Neville House Ministry of Defense London, United Kingdom	28-29 March 1990	No
3rd	Cascades Conference Center Williamsburg, Virginia	31 July - 2 August 1990	Yes
4th	Ministry of Defense Madrid, Spain	15-16 October 1990	Yes
5th	Federal Conference Centre Ottawa, Canada	14-17 May 1991	Yes
6th	Holiday Inn Diegem, Belgium and NATO Headquarters Brussels, Belgium	8 September 1991 9-11 September 1991	Yes
7th	Highbullen Hotel Chittlehamholt United Kingdom	1-4 June 1992	Yes
8th	NATO Headquarters Brussels, Belgium	20-21 October 1992	Yes
9th	Centre de Recherches du Service de Sante des Armees La Tronche, France	8-11 June 1993	Yes

minutes were distributed to the members of PG-29 for comment and consideration. The finalized version of the minutes, which incorporated all changes requested by PG-29, was prepared during or shortly after the conclusion of the next PG-29 meeting. Finalized minutes were submitted to the PG-29 Chairman at the DNA, who in turn submitted the minutes to NATO for official publication.

Starting with the 4th PG-29 meeting, a comprehensive record of discussions was prepared for each meeting. Unlike the official meeting minutes, which were intended for publication and distribution throughout NATO, the records of discussions were controlled-distribution documents intended for PG-29 members only. The records

of discussions described all discussions held, including those that included or were based on proprietary information. Rationales were presented for all decisions reached during the meeting. Attached as appendixes to records of discussions were approved meeting agendas, detailed listings of all action items, and relevant supporting materials that were not distributed as hand-outs during the PG-29 meetings. The records of discussions are used by PG-29 as reference documents.

4.3.1.2 NATO Documents. Three NATO documents, which are specific to the conduct and activities of PG-29, were prepared and/or revised as part of the Acute Radiation Sickness Amelioration Analysis. The finalized versions of these documents have been published as official NATO documents.

NATO Army Armaments Group Project Group 29 on Drug(s) for the Prevention and Treatment of Radiation-Induced Nausea and Vomiting Terms of Reference (NATO Army Armaments Group, 1991a) was begun prior to the start of the Acute Radiation Sickness Amelioration Analysis and completed during the 4th PG-29 Meeting in October 1990. A revision was made to this document at the 6th PG-29 Meeting in September 1991. A minimal role was played by SAIC in preparation of this document.

The *NATO Staff Requirement (NSR) for a Drug for the Prevention and Treatment of Radiation-Induced Nausea and Vomiting* (NATO Army Armaments Group, 1991b) was begun prior to the start of the Analysis and completed during the 4th PG-29 Meeting in October 1990. Preparation of this document included word processing, editorial review, and suggested modifications to the text.

The *Statement of Work for the Selection of a Drug for the Prevention and Treatment of Radiation-Induced Nausea and Vomiting* (NATO Army Armaments Group, 1992) was begun at the 4th PG-29 Meeting in October 1990 and completed at the 7th PG-29 Meeting in June 1992. Preparation of this document included: identification of studies required for military and civilian regulatory agency approvals, preparation of draft study descriptions, development of a draft program timeline, and development of an appropriate document format, word processing, and editing of text. This document is considered unique, since it is the first NATO Project Group Statement of Work to address development of a medical product.

4.3.1.3 Interim Status Reports. During the 6th PG-29 Meeting in September 1991, a record of the Project Group's progress in evaluating candidate 5-HT3 receptor antagonist anti-emetic drugs was begun. During the 7th PG-29 Meeting in June 1992, it was decided by PG-29 that the status report would be updated after the conclusion of each PG-29 meeting with each version of the document superseding the previous version. Included in each version was the current state of PG-29 knowledge regarding efficacy, side effects of potential military significance, toxicity, recommended oral dosing regimen, compatibility with other drug regimens, and civilian regulatory status.

The finalized version of *Interim Status Report Number 1 on Development of 5-HT3 Receptor Antagonist Anti-Emetic Drugs by NATO Project Group 29* was an 8-page document that included two tables. The finalized version of Interim Status Report Number 3 was a 40-page, fully-referenced document with three tables and six annexes. The draft

version of Interim Status Report Number 4, which was prepared and distributed subsequent to the 9th PG-29 Meeting in June 1993, included seven annexes. In each instance, a draft version of the status report was prepared subsequent to the conclusion of a PG-29 meeting and distributed to the members of PG-29 for comment and consideration. The finalized version of the report, which incorporated all changes requested by PG-29, was prepared shortly after the conclusion of the following PG-29 meeting. All Interim Status Reports contained proprietary information and were prepared as controlled-distribution documents.

4.3.1.4 PG-29 Guidelines. To ensure that the data for various human studies conducted under PG-29 sponsorship in different nations are collected and reported in an acceptable manner, two guidelines were prepared for publication as official PG-29 documents. The intent was to obtain all data required by PG-29 for evaluation of candidate anti-emetic drugs in a form suitable for submission to civilian drug regulatory agencies.

Guideline for Preparation of Final Study Reports for Human Studies Sponsored by NATO Army Armaments Group Project Group 29 on Drugs for the Prevention of Radiation-Induced Nausea and Vomiting was based on published FDA guidelines for preparation of New Drug Applications (U.S. Food and Drug Administration, February 1987a; U.S. Food and Drug Administration, February 1987b; U.S. Food and Drug Administration, July 1988). A draft version of the guideline was prepared and distributed to the members of PG-29 for comment and consideration. The finalized version, which incorporated all changes requested by PG-29, was prepared shortly after the conclusion of the 8th PG-29 Meeting in October 1992 and provided to the PG-29 Chairman at the DNA for submission to NATO.

Guideline for Collection of Data on Adverse Events and Biochemical Changes for Human Studies Sponsored by NATO Army Armaments Group Project Group 29 on Drugs for the Prevention of Radiation-Induced Nausea and Vomiting was based on data needs identified during the 8th PG-29 Meeting in October 1992. Once it became apparent that it was not possible to design a common data questionnaire for use in all PG-29-sponsored human studies, the concept of developing a guideline was raised. A draft version of the guideline was prepared and distributed to the members of PG-29 for comment and consideration. The guideline addressed the adverse events and biochemical changes that are of particular interest to PG-29, and the types of initial and follow-up data that should be collected when an adverse event occurs. The finalized version of the guideline, which incorporated all changes requested by PG-29, was prepared shortly after the conclusion of the 9th PG-29 meeting and provided to the PG-29 Chairman at the DNA for submission to NATO.

4.3.2 Triservice PG-29 Statement of Work Review Meetings.

Two Triservice Meetings hosted by the U.S. Army Nuclear and Chemical Agency (USANCA) were conducted in which the PG-29 Statement of Work was reviewed in preparation for Triservice staffing at the level of the Services' Surgeons General. In support of these meetings, draft minutes and U.S.-recommended modifications to the PG-29 Statement of Work were prepared. The draft minutes and Statement of Work

modifications were submitted to the U.S. Military Representative to PG-29, who was stationed at USANCA.

4.3.3 Radiation Risk/Safety Program Technology Transfer Meetings.

As part of the effort to keep DNA, other DoD agencies, and participating contractor organizations well informed, an annual meeting is held by the DNA Radiation Risk/Safety Program. In support of the 2nd Annual Technology Transfer Meeting in December 1991 and the 3rd Annual Technology Transfer Meeting in December 1992, a color exhibit highlighting the key features and timeline of the DNA anti-emetic drug development program was designed and constructed. The exhibit portrays how the military drug development program leverages ongoing commercial drug development efforts.

SECTION 5

IMPACT OF ACCOMPLISHMENTS

5.1 SELECTION OF CANDIDATE DRUGS.

The Acute Radiation Sickness Amelioration Analysis helped PG-29 in its timely selection of two candidate drugs by providing the Project Group with news of worldwide 5-HT3 receptor antagonist drug development efforts, recently published research results, and the suggestion that a precise definition of "candidate drug" be adopted. Subsequent to the selection of the two candidate drugs, PG-29 was able to focus its member nations' resources on the drug evaluation process.

5.2 PROGRESS OF PROJECT GROUP.

It is currently anticipated that PG-29 will be the first Project Group to complete its Statement of Work and report back to the NAAG in the 5-year timeframe allotted for a Project Group's charter. The progress of the Project Group is presented in each version of the Interim Status Report, and is reviewed in detail within the Record of Discussions prepared for each PG-29 Meeting. At the 9th PG-29 Meeting in June 1993, plans for maintaining tighter control over PG-29 milestones were devised.

5.3 PREPARATION OF THE PG-29 FINAL REPORT.

Through the efforts of the Acute Radiation Sickness Amelioration Analysis, the Interim Status Report developed into an evolving document that can be used as the blueprint for preparation of the PG-29 Final Report, which is scheduled for presentation to the NAAG in mid-1996. The references cited in the Status Report have been maintained in a separate hardcopy file for eventual retrieval and compilation as supporting appendixes to the PG-29 Final Report. At the 9th PG-29 Meeting in June 1993, plans were made to contact the NAAG regarding the format requirements for Final Report preparation.

SECTION 6

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APPENDIX A

GLOSSARY OF TERMS

ADVERSE EVENT. An undesired drug effect.

ANTI-EMETIC DRUG. A drug that prevents or reduces the severity of nausea and vomiting.

COMPARATOR DRUG. A drug with a known spectrum of activity that is used as a positive control for comparisons in investigational drug trials.

CYTOTOXIC. Capable of killing cells.

CYTOTOXIC CHEMOTHERAPY DRUGS. Drugs that promote the killing of cancer cells.

DOSING INTERVAL. The period of time between subsequent dose administrations.

DOSE-RESPONSE CURVE. Graphic depiction of a given quantitative response at different dose levels.

DOSE-RESPONSE LINE. Graphic depiction of the responses detected at different dose levels.

DRUG DEVELOPMENT. The process of testing investigational drugs for safety and efficacy, and submitting applications to drug regulatory agencies.

EFFICACY. Innate effectiveness.

EMESIS. Retching and Vomiting.

INVESTIGATIONAL DRUG. A drug not approved for marketing by drug regulatory authorities such as the U.S. Food and Drug Administration.

NEUROTRANSMITTER. A chemical substance released by neuronal cells that leads to the electrical excitation or inhibition of neighboring neuronal cells.

PLACEBO. An inert substance that is used as a negative control for comparisons in investigational drug trials.

SEROTONIN. 5-Hydroxytryptamine; a neurotransmitter

SEROTONIN TYPE-3 RECEPTOR. A type of serotonin receptor that differs from other serotonin receptor types in structure and function, and drug binding characteristics.

SEROTONIN TYPE-3 RECEPTOR ANTAGONIST. Drugs or compounds that prevent the actions produced by the neurotransmitter serotonin at serotonin type-3 receptors.

APPENDIX B

LIST OF ABBREVIATIONS AND ACRONYMS

DNA	Defense Nuclear Agency
NAAG	NATO Army Armaments Group
PG-29	Project Group 29
USANCA	U.S. Army and Nuclear Chemical Agency
TBI	Total Body Irradiation
ADME	Absorption, Distribution, Metabolism, and Elimination
NSR	NATO Staff Requirement
SAIC	Science Applications International Corporation
DoD	Department of Defense

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NAWCWPNSDIV DETACHMENT
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NUCLEAR WEAPONS TNG GROUP, PACIFIC
ATTN: CODE 32

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ATTN: NOP 06D
ATTN: NOP 50
ATTN: NOP 60
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OPERATIONAL TEST & EVALUATION FORCE
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PLANS, POLICY & OPERATIONS
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