ANNEX G TO SMALLPOX RESPONSE PLAN 29 September 2002
MEDICAL CARE OF SMALLPOX PATIENTS (VARIOLA INFECTION).

REFERENCES.

a. CDC Smallpox Response Plan, Annex 1. Overview Of Smallpox, Clinical Presentations, and Medical Care of Smallpox Patients, 23 September 2002. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/.

b. United States Army Medical Command. How-To" Guide for Command Surgeons: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

c. United States Army Medical Command. "How To" Guide for Unit Leaders and Unit Health Care Providers: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

d. United States Army Medical Command. "How To" Guide for Investigational New Drug (IND) Protocols, Supplement: Cidofovir (Vistide®, Gilead) to Treat Variola Infection (IND # 65,480). Falls Church, VA, publication pending.

e. CDC Smallpox Response Plan, Annex 2, Guidelines for Smallpox Vaccination Clinics, 23 September 2002. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/.

f. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med* 2002; 346:1300-8. http://content.nejm.org/cgi/reprint/346/17/1300.pdf.

g. Army Regulation 40-535, Air Force Regulation 164-5, OPNAVINST 4630.9C, MCO P4630.9A. Worldwide Aeromedical Evacuation. 10 May 1979. http://www.usapa.army.mil/pdffiles/r40_535.pdf.

1. General. This DoD Annex augments CDC Annex 1 (reference a). Appendix G-1 summarizes CDC Annex 1 and this DoD Annex on one page.

a. Mission. Health-care workers will render supportive and life-sustaining care to treat patients diagnosed with smallpox (variola infection).

b. Assumptions.

(1) Although smallpox can spread widely across human populations, control measures will eventually slow and then stop epidemic spread. Depending upon the method, extent, and duration of smallpox transmission, restriction and control of the ensuing epidemic will be effective.

(2) Variola infection is not inevitably fatal. About 70% of unvaccinated people will survive, as will ~ 98% of vaccinated people. Adequate, conscientious, modern medical support may raise these survival probabilities (Appendix G-3).

(3) The US Army Medical Research & Materiel Command (USAMRMC) applied to the Food & Drug Administration (FDA) for permission to use the antiviral medication cidofovir (*Vistide*, Gilead Sciences, www.gilead.com/wt/sec/vistide) under an investigational new drug (IND) protocol to treat human variola infections. FDA accepted this IND protocol in Sep 02.

(4) Vaccinia immune globulin (VIG) is of no value and has no role in treating smallpox (variola infection).

c. Planning Factors.

(1) Disease Progression. Appendix G-2 outlines the clinical development of variola infection (smallpox). Medical management of a patient with smallpox is mainly supportive (Appendix G-3).

(2) Clinical Care. Good care consists of (a) isolation of the patient to prevent transmission of the smallpox virus to non-immune people, (b) monitoring and maintaining fluid and electrolyte balance, (c) skin care, and (d) monitoring for and treatment of complications. Unless the diagnosis of smallpox is laboratory confirmed, vaccinate the patient if he or she will be isolated with other confirmed or suspected smallpox cases. Vaccination of suspected cases of smallpox is done to prevent the accidental transmission of smallpox virus to any suspected smallpox patients who have been misdiagnosed as smallpox cases. See also Appendix G-3.

(3) Education and Awareness. Education and training of specialized treatment teams (T-Teams) must occur before a smallpox outbreak occurs. The education of healthcare providers of all specialties about the existence of specialized treatment teams will be necessary for timely alert and communication. Informing the military leadership and the public about these T-teams will aid morale.

(4) Training. Specialized treatment teams will be trained in the requirements of IND protocols in general and the cidofovir treatment protocol in particular, to allow prompt use of this agent. The US Army will coordinate such training.

(5) Personnel Resources. Services will be prepared to augment MTF medical capabilities overwhelmed by a large number of smallpox cases. MTF commanders will develop procedures for emergency credentialing of healthcare workers to assist with disease outbreaks. The specialized treatment team will travel to the MTF with the initial smallpox patients. The gaining MTF will assign additional personnel to the specialized treatment team, as requested by the treating physician(s). Additional DoD assets will be assigned, if requirements extend beyond the capabilities of the local MTF. Appendix G-6 provides additional considerations in mass care of smallpox patients.

(6) Access to Cidofovir.

(a) MTFs will not use on-hand stocks of cidofovir to treat patients infected with variola virus, nor order cidofovir from other sources, without first coordinating with the US Army Medical Research Institute of Infectious Diseases (USAMRIID). Upon notification that a smallpox outbreak has occurred anywhere in the world, all MTF pharmacies will sequester any stocks of cidofovir on hand to treat retinitis, and begin controlling the cidofovir as if it were a Schedule II narcotic (e.g., storage in a safe or vault, perpetual inventory). The pharmacy will dispense the drug only for its labeled indication, unless its use is pursuant to an FDA-accepted IND protocol.

(b) USAMRIID will establish a common point of access for telephonic requests for use of cidofovir for a named patient by a physician willing to comply with IND requirements (references b, c, and d). Access to cidofovir for eligible patients will be facilitated by specialized treatment teams (T-Teams). Healthcare providers from civilian institutions should contact the CDC Drug Service for cidofovir: CDC Drug Service, National Center for Infectious Diseases, Mail stop D-09, Atlanta, GA 30333; 404-639-3670, fax 404-639-3717.

(7) Other Medications. If therapy with cidofovir is ineffective, clinicians may be inclined to try other therapeutic modalities unavailable when routine smallpox vaccinations ceased in the 1970s and 1980s (e.g., interferons, other antivirals). Little or no data may exist to support the safety or effectiveness of such approaches and no Federal agency sanctions their use. Nonetheless, DoD clinicians reserve their individual prerogatives and responsibilities in the clinical practice of medicine for individual patients.

d. Coordinating Instructions.

(1) Command Relationships. The specialized treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

(2) Communication. Information will be conveyed to other external sources, including the media, only with command approval and using risk-communication principles. If working in coordination with local treatment teams, no information will be conveyed to other external sources, including the media, without approval of, or simultaneous presentation with, the coordinating agency (CONUS--CDC, OCONUS--WHO).

e. Legal Considerations.

(1) All use of IND agents will be performed in accordance with IRB-approved guidelines and FDA regulations (see references b, c, and d, and Appendix G-4). MTFs will provide personnel and supply resources to the specialized treatment teams to satisfy regulatory requirements.

(2) Smallpox outbreaks may occur OCONUS. Travel of personnel into or out of the involved region may become difficult or impossible, for medical, legal, or political reasons. US unified commands will provide access by specialized treatment teams to patient needing treatment, as well as security for these T-Teams.

2. Execution.

a. Concept of Operations.

(1) The treatment of smallpox will occur within local medical facilities. Evacuation of smallpox patients will be avoided or minimized, to reduce contact with the patient and further spread of disease.

(2) Smallpox patients will be hospitalized, if adequate facilities permit. Adequate infection-control procedures (Annexes C and G) will be paramount. Negative airflow rooms are warranted. Cohorting (i.e., sharing of rooms/facilities by patients with similar disease categories) is recommended. Given adequate medical observation (at least daily physician visits) and restriction of further exposures, minimal care or out-of-hospital care is possible. See also Appendix G-6.

(3) Cidofovir is a medication licensed by the FDA for treatment of cytomegalovirus (CMV) retinitis in people infected with the human immunodeficiency virus (HIV) [see Appendix H-3]. For a different use, cidofovir is an investigational, moderately toxic antiviral agent projected to be given intravenously once a week in the treatment of variola infection. Side effects, especially renal insufficiency, occur. Animal-challenge experiments show the efficacy of cidofovir against orthopoxviruses (the group of viruses that includes variola and vaccinia viruses). It is presently unknown whether cidofovir will be effective in treating human smallpox infection. Cidofovir should be administered by an FDA-registered principal investigator or subinvestigator. Patient consent must be obtained before administration under IND protocol. See also Appendix G-4, for exceptions for unconscious patients. Actual use of cidofovir under the FDA-accepted protocol is specified within the treatment protocol (reference d). This protocol addresses dosage, expected side effects, physiologic and laboratory monitoring, and regulatory and reporting issues.

(4) Because of the administrative burden of implementing an IND protocol, and this drug's intravenous route of administration, multidisciplinary specialized treatment teams will be assembled to travel to areas affected by an outbreak, to administer cidofovir and assist with patient care. Prior vaccination against smallpox will be a condition of membership on these teams. Such T-Teams will include:

(a) Team leader – Senior medical officer.

(b) One or more infectious disease or dermatology physicians.

(c) One or more intensive-care physicians.

(d) Pharmacy officer and technician.

(e) Laboratory officer and technician.

(f) Nursing support – Two or more ICU-trained nurses.

(g) Preventive-medicine/Occupational-health specialist (physician or senior technician)

(h) Preventive-medicine technician

(i) Communications specialist

b. Tasks and Responsibilities.

(1) Identification and specific diagnosis of patients with smallpox will be the responsibility of healthcare providers at the MTF level, in consultation with regional infectious-diseases, dermatology, and pathology specialists, as needed. MTFs will make every attempt, using organic assets, to exclude the more common and probable diagnoses (e.g., chickenpox, allergic reactions, insect bites), using the CDC Generalized Vesicular or Pustular Rash Illness Protocol. See Annex A for the sequence when initiating an alert to the possible presence of a patient with smallpox.

(2) MTF commanders will be responsible for transporting patients between MTFs; provision of ancillary supply and personnel resources to specialized treatment teams; pharmacy and laboratory support; and communication support.

(3) The service member's unit will be responsible for initial transportation to the first-level MTF. Once within the medical system, it will be the responsibility of the medical-evacuation system for further patient transportation as needed. Evacuation of smallpox patients will be avoided or minimized, to reduce contact with the patient and further spread of disease.

(4) The MTF will provide routine medical care in accordance with standard practice, with laboratory, pharmacy, radiology, and pathology support. If the patient is treated with cidofovir, the treating team will have responsibility for the completion and maintenance of records and reports, and the processing or packaging of pathologic or autopsy materials.

(5) Once a definite or probable diagnosis of smallpox has been made, attending physicians will consider whether cidofovir treatment may be appropriate, consulting with local or regional infectious-disease (ID) or dermatology physicians. For clinical consultation with orthopoxvirus specialists, physicians may telephone USAMRIID at 1-888-USA-RIID or 301-619-2257. Alternately, page the USAMRIID staff duty officer at

301-631-4393 or the USAMRMC staff duty officer at 301-619-6092. USAMRIID will coordinate with specialized treatment teams, which will travel to the MTF caring for the diagnosed smallpox patient. These teams will be responsible for the treatment of patients with the indicated medications. IND-specific procedures will be followed carefully. To request cidofovir for a named patient, refer to Annex I.

c. Reporting.

(1) T-team leaders will periodically brief the MTF commander on the status of patients with smallpox, at a frequency directed by the commander.

(2) IND protocol reports will be submitted as detailed in reference d.

3. Operational Constraints.

a. Equipment. MTFs caring for smallpox patients can be expected to provide care up to and including intensive-care support. MTFs may expect this requirement to include appropriate equipment (e.g., ventilators, dialysis machines) and pharmacy support (e.g., vasopressors, and routine antibiotics).

b. Training. T-Teams will be trained in the use and monitoring of therapy with cidofovir. The US Army will coordinate such training. Periodic alert exercises, without travel, will be performed at least quarterly to sustain team proficiency.

c. Surge Capacity. Depending on the size of the smallpox outbreak, the number of people infected with smallpox may exceed the ability of specialized treatment teams to care for those infected with smallpox. Augmentation of T-Teams may occur by one or more of the following:

(1) Assignment of one or more additional regional treatment teams by USAMRIID, to the affected MTF or area;

(2) Augmentation of the team by local physician, pharmacy, nursing, and laboratory assets, with oversight of cidofovir administration remaining under the purview of the initial team’s subinvestigators; or

(3) Coordination with local civilian response teams, as needed. See paragraph 5 below.

d. Control of IND Agents. MTF pharmacy support to specialized treatment teams will include storage (see below), control, and security for both cidofovir and locally available medications. Pharmacy assets on the specialized treatment teams will prepare and dispense cidofovir for the team’s use.

e. Notification. Emergency use of an investigational drug for a named patient will comply with notification requirements to U.S. Army Medical Command, in accordance

with Army Regulation 40-7 (Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991), paragraph 4-9, and comparable regulations in other military Services.

f. Security. MTFs will coordinate with local military and local law enforcement personnel to protect patients, medical personnel, and the IND medications.

4. Administration and Logistics.

a. MTFs will provide administrative support for protocol performance by the teams (e.g., office space, copying, automation, communication support).

b. Shipping and Distribution. Either the T-Teams will transport the cidofovir themselves, or they will coordinate with the US Army Medical Materiel Agency (USAMMA) for transportation (see Annex I).

c. Supply and Storage. Supplies of cidofovir, delivered from USAMRIID, will be stored and maintained by the MTF pharmacy under the appropriate room-temperature conditions (reference d).

5. Special Situations.

a. Treatment of Military Personnel and Beneficiaries in CONUS. Military personnel and beneficiaries in CONUS will receive treatment in local military MTFs. Infection-control principles call for patients with smallpox to be cared for in designated Type-C treatment facilities. See also Annex C. At the beginning of a smallpox outbreak, this would likely be the first hospital(s) to which such patients are admitted.

b. Relation to Civilian Facilities. Members of specialized treatment teams will probably not be licensed under state regulations to provide medical care outside of a federal MTF. State regulations may be waived in time of emergency. Cidofovir and other IND medications may not be shared with or diverted to people not registered under the protocol, without the detailed knowledge and explicit agreement of USAMRIID and the principal investigator (who may also need FDA agreement).

c. Treatment of Military Personnel and Beneficiaries Outside of CONUS. Military personnel and beneficiaries OCONUS will receive treatment in local MTFs. Members of specialized treatment teams will probably not be licensed, by national laws or regulations, to provide medical care outside of the military MTF. These laws and regulations may be waived in time of emergency. Local civilian institutions may provide care to military personnel and beneficiaries under applicable Status of Forces Agreements or other agreements. Cidofovir and other IND medications may not be shared with or diverted to people not registered under the protocol, without the detailed knowledge and explicit agreement of USAMRIID and the principal investigator (who may also need FDA agreement).

d. Treatment of Military Personnel and Beneficiaries in Transit. If a patient started on cidofovir at one MTF is transferred to another medical facility, a physician at the gaining institution may continue cidofovir administration only if he or she agrees to join the IND protocol as a subinvestigator and takes responsibility for fulfilling FDA regulations for conducting an FDA-accepted IND protocol.

APPENDIX G-1
Medical Care Of Smallpox Patients (Variola Infection) – Summary.

1. Smallpox (variola infection) is not inevitably fatal. About 70% of unvaccinated people will survive infection, as will 95% of vaccinated people. The existence of a possible specific treatment for the disease, cidofovir (*Vistide*, Gilead Sciences), may increase survival.

2. The US Army Medical Research & Materiel Command (USAMRMC) is applying to the Food & Drug Administration (FDA) for permission to use cidofovir (*Vistide*, Gilead Sciences, Appendix G-5, Appendix H-3) under an investigational new drug (IND) protocol to treat human variola infections. This annex assumes FDA will accept this IND protocol.

3. Because of the administrative burden of implementing an IND protocol, and this drug's intravenous route of administration, multidisciplinary specialized treatment teams will be assembled to travel to areas affected by a smallpox outbreak, to administer cidofovir and assist with patient care. Prior vaccination against smallpox typically will be a condition of membership on these teams.

4. Once a definite or probable diagnosis of smallpox has been made, attending physicians will consider whether cidofovir treatment may be appropriate, consulting with local or regional infectious-disease (ID) or dermatology physicians. The physicians may request use of cidofovir for a named patient by telephoning USAMRIID at 1-888-USA-RIID or 301-619-2257. Alternately, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092.

5. USAMRIID will coordinate with these specialized treatment teams (T-Teams), which will travel to the MTF caring for the diagnosed smallpox patient. IND-specific procedures will be followed carefully. The specialized treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

6. Specialized treatment team leaders will periodically brief the MTF commander on the status of patients with smallpox, at a frequency directed by the commander. Team leaders and IND investigators will submit IND protocol reports as required by the FDA.

APPENDIX G-2
Stages of Smallpox Infection.

Communic-ability	Exposure = Day 0	Symptoms	Day of Symptoms	Disease Progress
Not contagious	Day 1	No symptoms		Virus introduced to respiratory tract
	2			
	3			
	4			Virus appears in lymph nodes
	5			
	6			Virus replicates in lymph system
	7			
	8			
	9			
	10			
	11	First symptoms	Day 1	
	12		2	Fever, backache, headache, nausea, malaise, enanthem
	13		3	
Contagious	14		4	
	15	Rash	5	Macules (spots)
Very contagious	16		6	Papules (bumps, pimples)
	17		7	
	18		8	
	19		9	Vesicles (blisters)
	20		10	
Contagious	21		11	Pustules (pus-filled blisters)
	22		12	
	23		13	
	24		14	
	25		15	Scabs
Scabs contagious	26		16	
	27		17	
	28		18	
	29		19	
	30		20	
Not contagious	31		Scars	
	32			

From Fenn (2001, p.19), Breman & Henderson (2002), and Fenner et al (1988).

First symptoms may begin as soon as 7 days or as late as 17 days after exposure.

APPENDIX G-3
Considerations in Clinical Care of Variola Infection.

1. Fluid and Electrolyte Balance. During the vesicular and pustular stages of smallpox, patients may experience significant fluid losses and become hypovolemic or develop shock. Fluid loss can result from (a) fever, (b) nausea and vomiting, (c) decreased fluid intake due to swallowing discomfort from pharyngeal lesions, (d) body fluid shifts from the vascular bed into the subcutaneous tissue, and (e) massive skin desquamation in patients with extensive confluent lesions. Electrolyte and protein loss may also occur in these patients. Monitor fluid and electrolyte balance in hospitalized patients with appropriate oral or intravenous correction of imbalances. Encourage patients with less severe disease who do not require hospitalization to maintain good oral intake of fluids, educated on the signs/symptoms of hypovolemia/dehydration, and counsel them on when to seek medical attention if hypovolemia/dehydration occurs.

2. Skin Care. Keep the skin clean. Avoid rupturing vesicles or pustules. Do not apply salves or ointments. In general, allow scab lesions to heal and separate on their own. All scabs should separate by 3 to 4 weeks. But lesions on the palms and soles may persist longer than 3 to 4 weeks unless artificially removed. Bacterial superinfection of lesions may occur and should be treated with appropriate antibiotics.

3. Monitoring and Treatment of Complications. Several types of complications may occur during the course of a smallpox infection. These include: (a) hemorrhagic, (b) secondary bacterial infections, (d) corneal ulceration and/or keratitis, (d) arthritis or osteomyelitis variolosa, (e) respiratory, (f) encephalitis, (g) gastrointestinal, and (h) genitourinary. These complications and their treatment are described below.

a. Hemorrhagic. Minor hemorrhagic manifestations such as subconjunctival hemorrhages occur commonly in smallpox patients. If subconjunctival hemorrhages are isolated and not accompanied by consumption coagulopathy or active bleeding (e.g., decreasing hemoglobin, hematocrit, or platelets), no specific therapy is needed. However, if signs of more extensive hemorrhage are present (e.g., mucosal bleeding, bleeding into smallpox lesions, ecchymoses, hematemesis, hematuria), evaluate the patient for disseminated intravascular coagulation (DIC) and treat appropriately. Hemorrhagic complications may indicate a more severe form of the disease called hemorrhagic smallpox, which has a poor prognosis. Because of a high, sustained viremia coupled with mucosal hemorrhaging, these patients are highly infectious.

b. Secondary Bacterial Infections. Bacterial superinfections can include abscesses of skin lesions, pneumonia, osteomyelitis, joint infections, and septicemia. Perform laboratory diagnostics to help guide antibiotic therapy.

c. Corneal Ulceration and/or Keratitis. These complications occurred more frequently in hemorrhagic-type smallpox but were occasionally seen in the more typical ordinary-type smallpox. In a case series reported by Rao from Bombay in 1972, corneal ulcers

occurred in 1% of non-hemorrhagic type smallpox cases and keratitis occurred in 0.25%. Corneal ulcerations can appear around the second week of illness and begin at the corneal margins. Ulcers can heal rapidly, leaving a minor opacity, or on occasion, may cause severe corneal scarring. Keratitis and corneal ulceration was far more common in malnourished individuals. Topical idoxuridine has been used but its efficacy is undocumented.

d. Arthritis or Osteomyelitis Variolosa. This complication occurred in 1.7% of the cases in the Rao case series. It usually occurred after the 15th day, accompanied by a brief recurrence of fever during scabbing. The elbow is the most commonly affected joint. Symmetrical, bilateral involvement was frequently seen. This complication was most commonly due to viral infection of the metaphyses of growing bones. Most cases resolved without permanent deformity.

e. Respiratory. Viral bronchitis and pneumonitis can be common complications of severe smallpox. Treatment is symptomatic, treating hypoxemia with oxygen and/or intubation/ventilation as indicated. Secondary bacterial pneumonia can occur and should be treated with appropriate antibiotics as guided by laboratory diagnostics. Pulmonary edema is common in more severe forms of smallpox (i.e., hemorrhagic, flat-type), and should be treated with careful monitoring of oxygenation, fluid status, and blood pressure, with supplemental oxygen and diuretics administered as needed. Patients with cough during the first week of disease may transmit disease more readily than patients without cough. Patients who developed a cough after symptom day 10, when viral counts in secretions were lower, were not as infectious as those who developed coughs earlier.

f. Encephalitis. This complication occurred in about one out of every 500 cases of smallpox. It usually appeared between the sixth and tenth day of illness, when the rash was still in the papular or vesicular stage. During the smallpox era, this complication was a minor contributor to the case-fatality rate of variola major. Although sometimes slow, recovery was usually complete.

g. Gastrointestinal – Nausea and vomiting can occur in the earlier stages of smallpox, especially in the prodromal period before rash development and should be treated symptomatically. Diarrhea may occasionally occur in the prodromal period or in the second week of illness and should also be treated symptomatically. Acute distension of the stomach occurred rarely and was more common in infants. In some severe cases of smallpox (especially flat-type), extensive viral infection of intestinal mucosa occurred with sloughing of the mucosal membrane. Most of these cases were fatal.

h. Genitourinary System. Orchitis occurred in 0.1% of the Rao case series and was usually unilateral. Hematuria can be present in hemorrhagic type smallpox if bleeding into the pelvis of the kidney occurs.

4. Pathology.

5. For additional advice, seek appropriate medical consultations.

APPENDIX G-4
Exceptions to General Rule to Obtain Informed Consent for Unconscious or Incapacitated Patients.

1. PURPOSE. To describe conditions within federal regulation that provide for exceptions to the general requirement to obtain individual informed consent before use of investigational new drugs (IND).

2. FACTS.

a. Under normal circumstances, DoD health-care providers will obtain documentation of the individual informed consent of the recipients of investigational new drugs (INDs), under provisions of Title 21 Code of Federal Regulations (CFR) Section 50.20, 21 CFR 312, DOD Directive 3216.2 (Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research), and related regulations.

b. Under unusual circumstances, it may not be possible to obtain consent in this way. Individuals incapable of reaching their own reasoned decision on whether or not to grant consent include people incapacitated physically or mentally, such as people who are unconscious.

c. Title 21 CFR 50.23(a) specifies conditions for exception from the general requirement to obtain consent. Both the protocol investigator and a physician not otherwise participating in the IND protocol must certify in writing all the following:

(1) The human subject is confronted by a life-threatening situation necessitating the IND drug,

(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject,

(3) Time is not sufficient to obtain consent from the subject's legal representative, and

(4) There is no alternate method of approved or generally recognized therapy providing an equal or greater likelihood of saving the life of the subject.

d. If time is not sufficient to permit the physician not participating in the clinical investigation to render a review, it shall be made within 5 working days after use of the drug.

e. Title 10 United States Code (USC) Section 980 prohibits DoD research unless "the informed consent of the subject is obtained in advance" or "in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance." This law does not apply to the

situation of individuals described in paragraphs 2b and 2c above, because the use of the IND drug would be for a treatment purpose and with individual life-saving intent, rather than as a function of a "research" undertaking within the meaning of 10 USC 980. This understanding of 10 USC 980 is supported by applicable case law (*Doe v. Sullivan*, 756 F. Supp. 12 (DDC 1991), affirmed, 938 F.2d 1370 (CADC 1991)).

f. Title 10 USC 1107 and 21 CFR 50.23(d) establish rules for waiver of informed consent by the President for IND drug use in particular military operations. As indicated in the legislative history of 10 USC 1107, these requirements for a Presidential waiver are not applicable to standard medical practice in the United States, such as authority to provide life-saving treatment to unconscious or incapacitated patients.

g. Title 21 CFR 50.24 discusses exception from informed-consent requirements for research of emergent conditions where it is anticipated that subjects will not be able to give their informed consent as a result of their medical conditions. In other words, 21 CFR 50.24 addresses situations where a large fraction of subjects will be unable to provide consent. This situation is not currently anticipated for any IND drug under evaluation by the Department of Defense.

APPENDIX G-5
Information Paper Describing Cidofovir.

INFORMATION PAPER

DASG-HCA
23 July 2002

SUBJECT: Cidofovir as a Treatment Against Vaccinia or Variola Viruses

1. Purpose. To describe the availability and potential value of the antiviral medication cidofovir in treating adverse events after smallpox vaccination or smallpox infection itself.

2. Facts.

a. Background. Cidofovir is an antiviral medication manufactured by Gilead Sciences (Foster City, California) with the brand name *Vistide*.

b. Approved Use. The Food & Drug Administration (FDA) approved cidofovir for the treatment of a viral infection of the eye that occurs among people with acquired immune deficiency syndrome (AIDS). This infection is known as cytomegalovirus (CMV) retinitis (inflammation of the retina). CMV retinitis is a relatively uncommon condition, so the standard commercial market for cidofovir is relatively small. As a result, available inventories of cidofovir could be exhausted by sudden increases in demand for the product.

c. Investigational Uses. Cidofovir has been proposed as (1) a treatment for adverse events caused by vaccinia virus, the active ingredient in smallpox vaccine, and (2) a treatment for variola infection (i.e., smallpox infection). The FDA has not approved these uses, so organized efforts to use cidofovir for either of these uses must fall under the investigational new drug (IND) provisions of FDA regulation and federal law. The US Army Medical Research Institute of Infectious Diseases is finalizing two IND protocols, one to support each of the two proposed uses of cidofovir.

d. Antiviral Effects. Using cidofovir against vaccinia or variola viruses is credible, because of laboratory and animal studies, including a study showing that cidofovir protects mice against lethal aerosol or intranasal cowpox virus challenge. However, there is no human experience with using cidofovir either for treating vaccine side effects or for treating smallpox infection.

e. Clinical Application. The proposed dose of cidofovir is 5 mg/kg, so an average patient will require one vial. A patient weighing more than 75 kg will require a second vial. About half of treated patients will need a second dose 7 days after the first. Cidofovir is diluted in 100 ml sodium chloride 0.9% (a common intravenous fluid) before

IV infusion. To minimize kidney damage, the oral medication probenecid plus intravenous fluids for hydration are administered before the cidofovir dose.

f. Logistical Characteristics. Cidofovir is stored at controlled room temperature (20º to 25ºC, 68º to 77ºF) with brief excursions permitted between 15º to 30ºC (59º to 86ºF). The federal contract price is $481.32 per vial as of July 2002. Unopened vials have up to a 3-year shelf life.

g. Stockpiles. About 2,500 vials of cidofovir are included in the National Pharmaceutical Stockpile managed by the Centers for Disease Control & Prevention (CDC). The Department of Defense does not maintain stocks of cidofovir beyond the small inventory at military hospitals available to treat CMV retinitis patients. Suitable warehousing space exists at Fort Detrick and other military installations.

h. Projection for Vaccination Reactions. Assuming that one person among 10,000 people vaccinated against smallpox develops an adverse event treatable with cidofovir and that each of these people needs an average of 1.5 vials of cidofovir, 150 vials costing $72,300 would be needed to support each 1 million vaccinations.

i. Projection for Smallpox Treatment. Assuming that 1,000 smallpox patients would need an average of 1.5 vials of cidofovir each for treatment, 1,500 vials costing $723,000 would be needed to treat each 1,000 smallpox patients.

LTC John D. Grabenstein/DASG-HCA/703-681-5059

Approved by COL Randolph

APPENDIX G-6
Mass Patient Care of Smallpox Patients: Planning Considerations.

1. Reference: CDC Smallpox Response Plan, Annex 3, Smallpox Vaccination Clinic Guide, 23 September 2002. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/.

2. Planning parameters for managing the consequences of the release of smallpox will include a variety of factors. All planning efforts must work in conjunction with established federal support planning. The primary consideration needs to be for the rapid expansion of capacity. This can be accomplished in a number of ways.

a. Expand existing personnel capacity by augmenting staff. Expansion of physical capacity can be accomplished by opening closed beds, wards, and floors. Converting large, interior spaces into patient care areas can develop further capacity. Some potential sources for augmenting staff may require the establishment of a memorandum of understanding. This must be done ahead of time. In addition to these local sources, the Department of Health and Human Services is initiating planning for the development of local Volunteer Medical Reserve Corps. Note that augmentation needs for mass patient care are in addition to those required for a mass vaccination program.

b. Use auxiliary facilities (e.g., hotels, schools). An important consideration in planning for the use of auxiliary facilities is that those facilities may not be able to be used again as originally intended. The use of auxiliary facilities may require that some standards of care be relaxed. Two major steps are required here: (a) Moving non-smallpox patients and other occupants out and (b) moving resources In (e.g., personnel, portable equipment).

c. Home care may be suitable for the type X and type R patient cohorts described in Annex A and below. Plan for the three facility types recommended by the CDC in the referenced document.

3. Command and Control. All elements of command and control must be exercised regularly. Use the incident command system. Use a centralized Communications Control Center. Centralize control of medical logistics and equipment. Centralize control of transportation assets. Consider using non-traditional (alternate) means of emergency transportation, such as public transportation, for patient movement. Establish procedures for patient movement to appropriate facilities and mobility of healthcare providers to and from treatment facilities. Develop a family support center, in coordination with the American Red Cross, to disseminate information to family members of victims.

4. Personnel Requirements. Preparing for the consequences of a smallpox outbreak will require a significant number of personnel associated with each component of the response. Resources provided by Federal and State agencies will not be sufficient to offset the medical human-resource needs associated with a large-scale smallpox

outbreak. Appropriate staffing of health and medical requirements will be critical for the success of this operation. Develop a plan for coordination with other local, state and federal agencies to avoid “double counting” potential augmentation resources.

a. Address credentialing issues to allow non-local physicians and other care providers to legally practice within the jurisdiction.

b. Ensure that during a smallpox response, unlicensed personnel can be utilized under the supervision of licensed personnel. Consider auxiliary personnel to assist with mass care (e.g., medical, nursing, veterinary students).

c. Identify in-hospital providers and first responders who would respond to a smallpox case. Identify personnel mobilization points.

d. Maintain adequate support staff (e.g., laundry, housekeeping, central supply) to provide mass care.

e. Identify hospital-based infectious-disease specialists for disease consultation.

f. Establish separate staffing to maintain normal medical functions, such as labor and delivery and injury care.

g. Provide for the segregation of providers treating smallpox victims from other providers. Establish control procedures to prevent medical personnel from fleeing from or flooding into medical treatment facilities. Consider the potential loss of healthcare providers due to smallpox exposure or fear of smallpox exposure.

h. Provide for the welfare and safety of emergency workers. Auxiliary response personnel for a city may number 5,000 or more people. Establish a vaccination plan for healthcare providers, public health officials, and their families. Provide appropriate personal protective equipment and infection control measures for personnel and train people in their use. Develop family support plan for medical providers and response personnel. Develop plan for the housing, feeding, and clothing needs of emergency responders.

5. Clinical Treatment and Advice.

a. Train medical staff to recognize and manage smallpox patients. Special considerations include immune-compromised patients and patients with adverse vaccination reactions.

b. Provide treatment protocols. Develop triaging procedures for smallpox victims. Utilize telemedicine for consultation.

c. Prepare to maintain appropriate documentation in mass-care setting.

d. Establish a hotline number to distribute information to vaccine recipients about what a vaccination take should look like. Provide information to those whose vaccinations do not take, including information about where to get revaccination.

e. Be prepared to treat persons with adverse reactions to vaccination. These patients should seek clinical care, which will probably not be available at mass vaccination sites.

6. Mental Health Services.

a. Plan for mental health services for victims and their families.

b. Plan for mental health services for emergency workers and their families.

c. Plan for the management of the worried well and psychological counseling for them.

7. Patient Tracking.

a. Match patients with appropriate medical facilities and other pre-selected treatment locations.

b. Track patients at all facilities.

8. Facilities.

a. Plan for the three facility types described in Annex A (i.e., type C facilities for contagious smallpox patients; type X facilities for vaccinated febrile patients without rash; type R facilities for asymptomatic contacts).

b. Home care may be suitable for the cohorts X and R noted above.

c. Plan for admission procedures for smallpox patients into hospitals or established treatment facility. Establish a standardized community reporting method to report bed availability.

d. Establish plans for the expedient expansion of the existing healthcare system capacity. Use isolation beds within existing facilities. Maximize use of existing healthcare facilities, by augmenting staff. Consider secondary treatment centers for temporary augmentation of healthcare capabilities. Consider using long-term care facilities. Consider using warehouses or schools, keeping in mind that such use may render the facilities contaminated and may require extensive decontamination. Consider the use of neighborhood-based treatment centers versus centralized treatment centers. Establish procedures to staff, equip and transport personnel and victims to and from secondary treatment facilities. Establish procedures for the movement of patients not infected with smallpox to other locales (e.g., National Defense Medical System).

e. Ensure adequate monitoring of the food, air and water within medical treatment facilities.

f. Enforce strict infection-control procedures (Annex C) and decontamination procedures (Annex F).

9. Patient Isolation.

a. Identify personnel responsible for local coordination of activities.

b. Identify appropriate facilities to be utilized for isolation and care.

c. Identify appropriate law-enforcement entities to enforce isolation and to control access to facilities.

d. Review and coordinate plan with Annex A.

10. Security. Provide security for medical treatment facilities and medical personnel (e.g., crowd control, preventing a rush of individuals wanting treatment and vaccinations). Provide security for medical supplies.

11. Training and Exercises.

a. Train personnel regarding the clinical aspects of a smallpox response.

b. Train healthcare and civilian personnel regarding the principles of homecare.

c. Train personnel on proper isolation techniques.

d. Exercise mechanisms to adapt and expand existing facilities.

e. Exercise all components of the local response system.

12. Planning Considerations for Mass Fatality Management.

a. Plan for vaccinating mortuary personnel and their families.

b. Maximize use of existing facilities.

c. Establish plans for the use of non-traditional facilities to augment existing facilities (e.g., cold storage, refrigerated vans).

d. Establish plans for requesting deployment of NDMS/DoD assets (e.g., portable morgue facilities and personnel to augment local capability).

e. Establish plans to identify the deceased. Prepare for and provide appropriate documentation.

f. Establish decontamination and isolation procedures for terminal-care providers.

g. Establish containment procedures for the deceased, following established protocols for double-body bagging/double taping. Exclude embalming procedures.

h. Consider use of vaults for burial purposes, if they are available and can handle more than one body. Do not use above-ground mausoleums.

i. Establish plans for engaging the religious community.