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November 29, 2004

Mr. John Becher
Centers for Disease Control/Drug Service, D-09
1600 Clifton Road
Atlanta, GA 30333

COL John D. Grabenstein, RPh, Ph.D.
Deputy Director for Military Vaccines
U.S. Army Medical Command
5111 Leesburg Pike (Suite 401)
Falls Church, VA 22041-3258

**Re: STN 101106 -Smallpox Vaccine, Dryvax®**

Dear Mr. Becher and Colonel Grabenstein:

This is to inform you that Labeling Supplement STN 101106/5057, which contains revisions to the Dryvax® Physician's Package Insert that reflect updated safety information related to myopericarditis and includes a black box warning, was approved by the FDA on November 5, 2004.

The updated Package Insert text (see attached) has been posted on the FDA's Web site at http://www.fda.gov/cber/.

The black box warning reads as follows:

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**WARNINGS**

**ACUTE MYOPERICARDITIS HAS BEEN OBSERVED AFTER ADMINISTRATION OF DRYVAX® TO HEALTHY ADULTS (see WARNINGS and ADVERSE REACTIONS).**

**ENCEPHALITIS HAS OCCURRED FOLLOWING SMALLPOX IMMUNIZATION. PROGRESSIVE VACCINIA HAS OCCURRED AFTER SMALLPOX VACCINATION, ALMOST ALWAYS IN IMMUNOCOMPROMISED PERSONS. SEVERE VACCINIAL SKIN INFECTIONS FOLLOWING SMALLPOX VACCINATION HAVE OCCURRED AMONG PERSONS WITH ECZEMA. THESE COMPLICATIONS MAY RESULT IN PERMANENT SEQUELAE OR DEATH (see ADVERSE REACTIONS).**

**IMMUNOCOMPROMISED PERSONS, INCLUDING THOSE RECEIVING IMMUNOSUPPRESSIVE MEDICATIONS, PERSONS WITH ECZEMA, AND PERSONS WITH CARDIAC DISEASE SHOULD NOT RECEIVE DRYVAX® IN NON-EMERGENCY SITUATIONS (see CONTRAINDICATIONS).**

The need for a black box warning is based on additional reports of myopericarditis, both symptomatic and asymptomatic, from an ongoing clinical trial comparing Dryvax® and an investigational smallpox vaccine also derived from the New York City Board of Health vaccinia strain. Data combined for both vaccines has demonstrated a preliminary rate estimate for myopericarditis of 69 per 10,000 primary vaccinations, exceeding the rate estimate of 1.2 per 10,000 vaccinations following the use of Dryvax® in the Department of Defense 2002-2003 vaccination program.

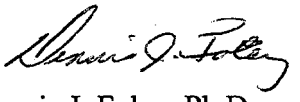
The **Warnings** and **Adverse Reactions** sections of the Package Insert have also been revised accordingly.

The **Indications and Usage** section has been modified to reflect this new safety information. The use of smallpox vaccine is now restricted to "persons determined to be at risk for smallpox infection."

Wyeth

Please inform all end users of these changes and of the availability of the updated Package Insert text on the FDA's Web site.

Sincerely yours,



Dennis J. Foley, Ph.D.

DJF:jm
enc.

cc: J. Goodman (CBER)
D. Staten (CBER)

# Smallpox Vaccine
# Dried, Calf Lymph Type

**Dryvax®**

**Dried Smallpox Vaccine**

℞ only

**WARNINGS**

**ACUTE MYOPERICARDITIS HAS BEEN OBSERVED AFTER ADMINISTRATION OF DRYVAX® TO HEALTHY ADULTS (see WARNINGS and ADVERSE REACTIONS).**

**ENCEPHALITIS HAS OCCURRED FOLLOWING SMALLPOX IMMUNIZATION. PROGRESSIVE VACCINIA HAS OCCURRED AFTER SMALLPOX VACCINATION, ALMOST ALWAYS IN IMMUNOCOMPROMISED PERSONS. SEVERE VACCINIAL SKIN INFECTIONS FOLLOWING SMALLPOX VACCINATION HAVE OCCURRED AMONG PERSONS WITH ECZEMA. THESE COMPLICATIONS MAY RESULT IN PERMANENT SEQUELAE OR DEATH (see ADVERSE REACTIONS).**

**IMMUNOCOMPROMISED PERSONS, INCLUDING THOSE RECEIVING IMMUNOSUPPRESSIVE MEDICATIONS, PERSONS WITH ECZEMA, AND PERSONS WITH CARDIAC DISEASE SHOULD NOT RECEIVE DRYVAX® IN NON-EMERGENCY SITUATIONS (see CONTRAINDICATIONS).**

**DO NOT INJECT INTRAMUSCULARLY (IM), INTRAVENOUSLY (IV), OR SUBCUTANEOUSLY (SC). FOR CONVENTIONAL SMALLPOX VACCINATION (SCARIFICATION) ONLY.**

## DESCRIPTION

Smallpox Vaccine, Dried, Calf Lymph Type, Dryvax®, is a live-virus preparation of vaccinia virus derived from the New York City Board of Health vaccinia strain, prepared from calf lymph. The calf lymph is purified, concentrated, and dried by lyophilization. During processing, polymyxin B sulfate, dihydrostreptomycin sulfate, chlortetracycline hydrochloride, and neomycin sulfate are added, and trace amounts of these antibiotics may be present in the final product. The reconstituted vaccine has been shown by appropriate test methods to contain not more than 200 viable bacterial organisms per mL.

The diluent for Dryvax® contains 50% glycerin, and 0.25% phenol in Sterile Water for Injection, USP.

The reconstituted vaccine, which contains approximately 100 million infectious vaccinia viruses per mL, is intended only for multiple-puncture use, ie, administration of the vaccine into the superficial layers of the skin using a bifurcated needle.

## CLINICAL PHARMACOLOGY

Introduction of potent smallpox vaccine containing infectious vaccinia viruses into the superficial layers of the skin results in viral multiplication, immunity, and cellular hypersensitivity. With the primary vaccination, a papule appears at the site of vaccination on about the 2$^{nd}$ to 5$^{th}$ day. This becomes a vesicle on the 5$^{th}$ or 6$^{th}$ day, which becomes pustular, umbilicated, and surrounded by erythema and induration. The maximal area of erythema is attained between the 8$^{th}$ and 12$^{th}$ day following vaccination (usually the 10$^{th}$). The erythema and swelling then subside, and a crust forms which comes off about the 14$^{th}$ to 21$^{st}$ day. At the height of the primary reaction known as the Jennerian response, there is usually regional lymphadenopathy and there may be systemic manifestations of fever and malaise.

Primary vaccination with product at a potency of 100 million pock-forming units (pfu)/mL elicits a 97% response rate by both major reaction (see **DOSAGE AND ADMINISTRATION, Interpretation of Responses:** *Major Reaction*) and neutralizing antibody response in children.[1,2] Immunity wanes after several years, and an allergic sensitization to viral proteins can persist. This allergy is manifested by the appearance of a papule and a small area of redness appearing within the first 24 hours after revaccination; this may be the maximum reaction but not infrequently vesicles appear in 24 to 48 hours with ultimate scabbing. The peak of this type of reaction is passed within three days following the application of fully potent vaccine with an antibody rise occurring in roughly half of those who exhibit such a reaction. As immunity wanes, revaccination with potent vaccine elicits this allergic response followed by the changes produced by propagating virus. The lesion may then go through the same course as the primary vaccination or may exhibit an accelerated development of the lesion and its attendant erythema. Viral propagation is assumed to have occurred (and an immune response evoked) when the greatest area of skin involvement (erythema) occurs after the third day following revaccination. Revaccination is considered successful if a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion, which may be a scar or ulcer, is present on examination 6-8 days after revaccination.[3]

## INDICATIONS AND USAGE

Smallpox vaccine is indicated for active immunization against smallpox disease for persons determined to be at risk for smallpox infection.

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination of laboratory workers who directly handle a) cultures or b) animals contaminated or infected with non-highly attenuated vaccinia virus, recombinant vaccinia viruses derived from non-highly attenuated vaccinia strains, or other Orthopoxviruses that infect humans (eg, monkeypox, cowpox, vaccinia and variola).[2] The ACIP also recommends that vaccination can be considered for healthcare workers who have contact with clinical specimens, contaminated materials (eg, dressings), or patients receiving vaccinia or recombinant vaccinia viruses. Risks associated with receipt of vaccine should be weighed against the risks of exposure to Orthopoxviruses.

For those in the above special-risk categories, revaccination is recommended at appropriate intervals (every ten years).[2]

Vaccination is not required for laboratory and other healthcare personnel who work with highly-attenuated poxvirus strains such as modified vaccinia Ankara (MVA), NYVAC (derived from the Copenhagen vaccinia strain), ALVAC (derived from the canarypox virus), and TROVAC (derived from fowlpox virus).[2]

The Armed Forces recommends use of smallpox vaccine for certain categories of personnel. See the most recent issue of Immunizations and Chemoprophylaxis, Departments of the Army, the Navy, the Air Force, and Transportation (Army Regulation 40-562, BUMEDINST 6230.15, Air Force Joint Instruction 48-110, CG COMDTINST M6230.4E)[4] and Department of Defense (DoD) Directive 6205.3[5] for current recommendations concerning use.

The judicious use of smallpox vaccine has eradicated naturally occurring smallpox. At the World Health Assembly in May 1980, the World Health Organization (WHO) declared the world free of (naturally occurring) smallpox.[6]

As with any vaccine, smallpox vaccine may not protect all individuals receiving the vaccine.

### Use of Smallpox Vaccine in Response to Bioterrorism:

Recommendations for use of smallpox vaccine for bioterrorism preparedness and response are periodically updated by the Centers for Disease Control and Prevention (CDC), and the most recent recommendations can be found at http://www.cdc.gov.

## CONTRAINDICATIONS

### Contraindications for Non-Emergency Vaccine Use

Primary vaccination AND revaccination with smallpox vaccine are contraindicated:

For any individuals who are allergic to any component of the vaccine, including polymyxin B sulfate, dihydrostreptomycin sulfate, chlortetracycline hydrochloride, and neomycin sulfate.

2. Infants <12 months of age. The ACIP advises against non-emergency use of smallpox vaccine in children <18 years of age.[2]

3. For individuals of any age with eczema or past history of eczema, other acute, chronic, or exfoliative skin conditions (eg, atopic dermatitis, wounds, burns, impetigo, or Varicella zoster). Household contacts of such persons should not be vaccinated.[2]

4. For persons of any age receiving therapy with systemic corticosteroids at certain doses (eg, ≥2 mg/kg body weight or ≥20 mg/day of prednisone for ≥2 weeks),[2] or immunosuppressive drugs (eg, alkylating agents, antimetabolites), or radiation. Household contacts of such persons should not be vaccinated.

5. For individuals with congenital or acquired deficiencies of the immune system, including individuals infected with the human immunodeficiency virus (HIV), leukemia, lymphoma, generalized malignancy, solid organ or hematopoietic stem cell transplantation, defects of cellular and/or humoral immunity. Household contacts of such persons should not be vaccinated.

6. During pregnancy, suspected pregnancy, or to household contacts of pregnant women.

7. Persons with known cardiac disease, including those diagnosed with previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest pain or shortness of breath with activity, or other heart conditions being treated by a doctor, should not receive vaccination in non-emergency situations.

The most recent CDC recommendations for the use of smallpox vaccine can be found at http://www.cdc.gov.

### Contraindications for Smallpox Emergency

There are no absolute contraindications regarding vaccination of a person with a high-risk exposure to smallpox.[2] Persons at greatest risk for experiencing serious vaccination complications are often those at greatest risk for death from smallpox. If a relative contraindication to vaccination exists, the risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.[2]

## WARNINGS

### Myopericarditis

There is an increased risk of acute myopericarditis following vaccinia smallpox vaccinations (see **ADVERSE REACTIONS**).

In a recent clinical trial among primary vaccinees comparing Dryvax and an investigational smallpox vaccine also derived from the New York City Board of Health vaccinia strain, 8 cases of suspected or probable myopericarditis, including both symptomatic and asymptomatic cases, were detected when active monitoring was used. These cases occurred among 1,162 subjects enrolled in the combined study groups. The corresponding preliminary rate estimate of myopericarditis is 1 in 145, or 69 per 10,000 primary vaccinations[7] (see **ADVERSE REACTIONS**).

Probable or confirmed cases of myopericarditis following the use of Dryvax were reported in the Department of Defense 2002-3 vaccination program.[8] The mean time from vaccination to evaluation for myopericarditis was 10.4 days (range 3-25 days). Sixty-seven symptomatic cases were identified from a total of 540,824 military vaccinees, a rate of 1.2 per 10,000 vaccinations. Fifty-seven patients were evaluated with echocardiography during the acute illness. Thirty-two percent had mild to moderate depression of ejection fraction, and 12% had pericardial effusion. At follow-up echocardiography (N=40), no patient had an ejection fraction <54%, and no patient had evidence of ventricular dilatation, diastolic dysfunction, regional wall motion abnormality, or pericardial effusion. Fourteen percent of patients reported continued subjective symptoms, including chest discomfort, fatigue, and headache[8] (see **ADVERSE REACTIONS**).

The long-term complications of myopericarditis following Dryvax vaccination, if any, are currently unknown.

Ischemic cardiac events, including fatalities, have been reported following routine non-emergency vaccine use; the relationship of these events, if any, to Dryvax is unknown. The non-emergency use of Dryvax has not been recommended for persons with certain risk factors for cardiac disease (see http://www.cdc.gov).

Cases of non-ischemic, dilated cardiomyopathy have been reported following vaccination.[9] The relationship of these cases to vaccination with Dryvax, if any, is uncertain.

## PRECAUTIONS

### General

The vial stopper contains dry natural rubber that may cause hypersensitivity reactions when handled by, or when the product is administered to, persons with known or possible latex sensitivity.

After completion of the multiple-puncture vaccination, blot off any vaccine remaining on skin at vaccination site with clean, dry gauze or cotton.

The vaccine vial, its stopper, the needle to release the vacuum, the diluent syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be burned, boiled, or autoclaved before disposal.

Individuals susceptible to adverse effects of vaccinia virus, eg, those with eczema, immunodeficiency states, including HIV infection, should be identified and measures taken to avoid contact with persons with active vaccination lesions. Contact spread of vaccinia from recently vaccinated military personnel has been reported[10,11,12] (see **ADVERSE REACTIONS**).

*Prevention of contact transmission of vaccinia*

Vaccinia virus may be cultured from the site of primary vaccination beginning at the time of development of a papule (2 to 5 days after vaccination) until the scab separates from the skin lesion (14 to 21 days after vaccination). During this time, care must be taken to prevent spread of the virus to another area of the body or to another person. The vaccination site may be left uncovered or can be covered with a porous bandage, such as gauze, until the scab has separated and the underlying skin has healed. An occlusive bandage should not be routinely used. If a bandage is used to cover the vaccination site, it should be changed frequently (ie, every 1-2 days) to prevent maceration of the vaccination site secondary to fluid accumulation. No salves or ointments should be used on the vaccination site. Contaminated bandages should be placed in sealed plastic bags before disposal in the trash. Clothing or other cloth materials that have had contact with the site can be decontaminated with routine laundering in hot water with bleach.[2] The vaccination site should be kept dry, although normal bathing can continue.[2]

Recently vaccinated healthcare workers should avoid contact with patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with patients is essential and unavoidable, they may continue to have contact with patients, including those with immunodeficiencies, as long as the vaccination site is well covered and good hand-washing technique is maintained by the vaccinee. In this setting, a more occlusive dressing may be required. Semipermeable polyurethane dressings (eg, Opsite®) are effective barriers to vaccinia and recombinant vaccinia viruses. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral spread when the dressing is removed. In addition, accumulation of fluid beneath the dressing may increase the maceration of the vaccination site. Accumulation of exudate may be decreased by first covering the vaccination with dry gauze, then applying the dressing over the gauze. The dressing should also be changed at least once a day.

The most important measure to prevent inadvertent implantation and contact transmission from vaccinia vaccination is thorough hand washing after changing the bandage or after any other contact with the vaccination site.

*Simultaneous administration with other live-virus vaccines*

There are no data evaluating the simultaneous administration of smallpox vaccine with other live-virus vaccines.

## PREGNANCY

### Pregnancy Category C

Animal reproduction studies have not been conducted with smallpox vaccine. Smallpox vaccine should not be given to pregnant women in routine, non-emergency conditions. For emergency conditions, see **CONTRAINDICATIONS – Contraindications for Smallpox Emergency** and **INDICATIONS AND USAGE – Use of Smallpox Vaccine in Response to Bioterrorism.**

On rare occasions, vaccinia virus has been reported to cause fetal infection. Affected pregnancies have been reported among first-time vaccinees, revaccinees, and among unvaccinated close contacts of vaccinees.[13] Fetal vaccinia usually results in stillbirth or death of the infant shortly after delivery. Vaccinia vaccine is not known to cause congenital malformations.[2] Among 185 live births born to vaccinated mothers followed in the CDC pregnancy registry, there have been no reports of fetal vaccinia. Five infants with differing congenital anomalies were reported.[14] The overall rate of congenital malformations does not appear to exceed background rates.[2]

Healthcare providers, state health departments, and other public health staff are encouraged to report to the National Smallpox Vaccine in Pregnancy Registry all cases in which women received smallpox vaccine during pregnancy or within 42 days prior to conception, or were closely exposed to a vaccinee within 28 days after vaccination.[15] Civilian women should contact their healthcare provider or state health department for help enrolling in the registry. Clinicians or public health staff should report civilian cases through their state health department or to CDC, telephone 404-639-8253 or 877-554-4625. Military cases should be reported to the DoD, telephone 619-553-9255, Defense Switched Network (DSN) 553-9255, fax 619-553-7601 or e-mail code 25@nhrc.navy.mil.

### Nursing Mothers

It is not known whether vaccine virus or antibodies are excreted in human milk. This vaccine is not recommended for use in a nursing mother in non-emergency situations. For use in emergency situations, see **CONTRAINDICATIONS – Contraindications for Smallpox Emergency.**

### Pediatric Use

Before the eradication of smallpox disease, smallpox vaccination was administered routinely during childhood. However, pediatric use of smallpox vaccine is not recommended for use in non-emergency situations and is contraindicated for infants <12 months in non-emergency situations. For use in emergency situations, see **CONTRAINDICATIONS – Contraindications for Smallpox Emergency.**

### Geriatric Use

There are no published data to support the use of this vaccine in geriatric populations. This vaccine is not recommended for use in geriatric populations in non-emergency conditions. For use in emergency conditions, see **CONTRAINDICATIONS – Contraindications for Smallpox Emergency.**

## ADVERSE REACTIONS

A fever is common after vaccinia vaccination is administered. Up to 70% of children have one or more days of temperature ≥100°F from 4 to 14 days after primary vaccination, and 15% to 20% have temperatures of ≥102°F. After revaccination, 35% of children develop temperatures of ≥100°F, and 5% have temperatures of ≥102°F. Fever is less common in adults than children after vaccination or revaccination.[2]

Generalized rashes (erythematous, urticarial, nonspecific) and secondary pyogenic infections at the site of vaccine applications may occur. Rarely bullous erythema multiforme (Stevens-Johnson syndrome) occurs.[2]

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination, usually resulting from autoinoculation of the vaccine virus transferred from the site of vaccination. The most common sites involved are the face, eyelid, nose, mouth, genitalia, and rectum. Accidental infection (autoinoculation) of the eye may result in blindness.

Generalized vaccinia among persons without underlying illnesses is characterized by a vesicular rash of varying extent. The rash is generally self-limited and requires little or no therapy except among patients whose conditions appear to be toxic or who have serious underlying illnesses.[2] Contact spread of vaccinia from recently vaccinated military personnel has been reported (see **CONTRAINDICATIONS**).[10,11,12]

More severe complications that may follow either primary vaccination or revaccination include: postvaccinial encephalitis, encephalomyelitis, encephalopathy, myopericarditis,[16] progressive vaccinia (vaccinia necrosum), and eczema vaccinatum. Such complications may result in severe disability, permanent neurological sequelae, and/or death.[17,18] Although a rare event, approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations have occurred after vaccinia vaccination. Death is most often the result of postvaccinial

encephalitis or progressive vaccinia.[2,19] Death has also been reported in unvaccinated contacts of individuals who have been vaccinated.[19]

### Myopericarditis

In a recent clinical trial among primary vaccinees comparing Dryvax and an investigational smallpox vaccine also derived from the New York City Board of Health vaccinia strain, 8 cases of suspected or probable myopericarditis, including both symptomatic and asymptomatic cases, were detected when active monitoring was used. These cases occurred among 1,162 subjects enrolled in the combined study groups. The corresponding preliminary rate estimate of myopericarditis is 1 in 145, or 69 per 10,000 primary vaccinations.[7]

Probable or confirmed cases of myopericarditis following the use of Dryvax were reported in the Department of Defense 2002-3 vaccination program.[8] The mean time from vaccination to evaluation for myopericarditis was 10.4 days (range 3-25 days). Sixty-seven symptomatic cases were identified from a total of 540,824 military vaccinees, a rate of 1.2 per 10,000 vaccinations. Fifty-seven patients were evaluated with echocardiography during the acute illness. Thirty-two percent had mild to moderate depression of ejection fraction, and 12% had pericardial effusion. At follow-up echocardiography (N=40) no patient had an ejection fraction <54%, and no patient had evidence of ventricular dilatation, diastolic dysfunction, regional wall motion abnormality, or pericardial effusion. Fourteen percent of patients reported continued subjective symptoms including chest discomfort, fatigue, and headache.[8]

As of May 9, 2003, 21 cases of myopericarditis had been reported to the Vaccine Adverse Event Reporting System (VAERS) among 36,217 persons who had been vaccinated with Dryvax as part of the civilian smallpox pre-event program.[20]

The reporting rates from the Department of Defense and civilian smallpox vaccination programs likely underestimate the true incidence of myopericarditis following Dryvax, especially cases of mild or subclinical disease, as cases were not prospectively collected through active monitoring in a clinical trial.

The long-term complications, if any, associated with myopericarditis following smallpox vaccination are unknown.

Ischemic cardiac events, including fatalities, may follow vaccine use; the relationship of these events, if any, to smallpox vaccination is unknown. The non-emergency use of Dryvax has not been recommended for persons with certain risk factors for cardiac disease (see http://www.cdc.gov).

Cases of non-ischemic, dilated cardiomyopathy have been reported following vaccination.[9] The relationship of these cases to vaccination with Dryvax, if any, is uncertain.

Estimates of the risks of occurrence of other serious complications after primary vaccination and revaccination based on safety surveillance studies conducted when smallpox vaccine was routinely recommended are as follows[21]:

**Rates of reported complications* associated with vaccinia vaccinations (cases/million vaccinations) †**

| Age (yrs) and status | Inadvertent inoculation§ | Generalized vaccinia | Eczema vaccinatum | Progressive vaccinia¶ | Postvaccinial encephalitis | Death[16,#] | Total** |
|---|---|---|---|---|---|---|---|
| *Primary vaccination* | | | | | | | |
| <1 | 507.0 | 394.4 | 14.1 | --†† | 42.3 | 5 | **1549.3** |
| 1-4 | 577.3 | 233.4 | 44.2 | 3.2 | 9.5 | 0.5 | **1261.8** |
| 5-19 | 371.2 | 139.7 | 34.9 | --†† | 8.7 | 0.5 | **855.9** |
| ≥ 20 | 606.1 | 212.1 | 30.3 | †† | --†† | unknown | **1515.2** |
| **Overall rates†** | **529.2** | **241.5** | **38.5** | **.5** | **12.3** | -- | **1253.8** |
| *Revaccination* | | | | | | | |
| <1 | --†† | --†† | --†† | --†† | --†† | | --†† |
| 1-4 | 109.1 | --†† | --†† | --†† | --†† | | **200.0** |
| 5-19 | 47.7 | 9.9 | 2.0 | --†† | --†† | | **85.5** |
| ≥ 20 | 25.0 | 9.1 | 4.5 | 6.8 | 4.5 | | **113.6** |
| **Overall rates§§** | **42.1** | **9.0** | **3.0** | **3.0** | **2.0** | | **108.2** |

† Adapted from Lane JM, Ruber FL, Neff JM, Millar JD. Complication of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis. 1970;122:303-309.
* See text for descriptions of complications.
§ Referenced as accidental implantation.
¶ Referenced as vaccinia necrosum.
# Death from all complications.[17]
** Rates of overall complications by age group include complications not provided in this table, including severe local reactions, bacterial superinfection of the vaccination site, and erythema multiforme.
†† No instances of this complication were identified during the 1968 10-state survey.
§§ Overall rates for each complication include persons of unknown age.

Complications of revaccination, while less frequent, do occur, especially in patients with underlying diseases or in patients receiving therapy that impairs immunologic competence, or in subjects who have not been vaccinated for many years. Subjects who have not been vaccinated for many years may respond as primary vaccinees with respect to both the local and systemic reactions to vaccine administration and risk of occurrence of the above-mentioned serious complications.[2]

The Centers for Disease Control and Prevention (CDC) can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia (smallpox) vaccination. Vaccinia Immune Globulin (VIG) is indicated for certain complications of smallpox vaccination. Several antiviral compounds have been shown to have activity against vaccinia virus or other orthopoxviruses in vitro and in animal models. However, insufficient information exists on which to base recommendations for any antiviral compound to treat postvaccination complications or Orthopoxvirus infections, including smallpox.[2] If VIG is needed or additional information is required, physicians should contact the CDC at (404) 639-3670, Monday through Friday 8AM to 4:30 PM Eastern Standard Time; at other times call (404) 639-2888.

The United States Department of Health and Human Services (DHHS) has established the Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events of any vaccine. The VAERS toll-free number for VAERS forms and information is (800-822-7967). The VAERS website is http://www.fda.gov/cber/vaers/vaers/htm.

## DOSAGE AND ADMINISTRATION

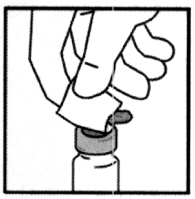
READ ALL DIRECTIONS COMPLETELY BEFORE BEGINNING RECONSTITUTION AND ADMINISTRATION. WHEN RECONSTITUTING AND ADMINISTERING THE VACCINE, USE PROTECTIVE GLOVES AND ASEPTIC TECHNIQUE.

### Directions for Reconstitution:

Note: The healthcare provider must have available a sterile 21 gauge or smaller needle to release the vacuum in the vials prior to adding diluent. This needle must only be used to release the vacuum. The needle to release the vacuum is NOT included in the kit.

1. Lift up tab of aluminum seal on vaccine vial. DO NOT BREAK OFF OR TEAR DOWN TAB.

2. Wipe off vial stopper with an alcohol sponge and allow to dry.



3. Place vaccine vial upright on a hard, flat surface. Insert a sterile 21 gauge or smaller needle into the rubber stopper to release the vacuum from the vaccine vial. Discard the needle in biohazard waste container.

4. To reduce viscosity of cold diluent, warm by holding diluent-cartridge in palm of hand for a minute or so.

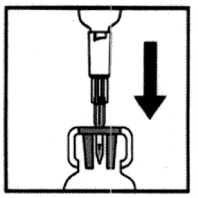
5. Peel open the vented needle package (provided with the kit) and aseptically remove the vented needle.

6. Remove rubber cover from end of the diluent syringe.

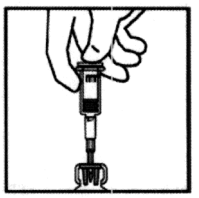
7 With a twisting motion, aseptically attach the vented needle to the hub of the diluent syringe.

8. Remove protective cover from the vented needle and expel the air from the diluent syringe.

9. Aseptically insert the needle through the rubber stopper into the vaccine vial up to the first hub.



10. Depress the plunger to ensure the entire volume of diluent is delivered into the vial.



11. Withdraw diluent syringe/vented needle and discard in biohazard waste container.

12. Allow vaccine vial to stand undisturbed for 3 to 5 minutes. Then if necessary, swirl vial gently to effect complete reconstitution.

13. Record date of reconstitution.

14. Store reconstituted vaccine at 2° to 8°C (36° to 46°F) when not in actual use. The vaccine may be stored for no more than 90 days after reconstitution based on viral potency testing.

### Sites of Vaccination:

The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle is the preferred site for smallpox vaccination.

### Method of Vaccination:

USE 2 OR 3 NEEDLE PUNCTURES FOR PRIMARY VACCINATION; 15 FOR REVACCINATION.

Reconstituted vials should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use vaccine if particulate matter or discoloration is present.

1 First pull down the "tear off" tab from the aluminum seal of the vaccine vial.

2. Remove entire aluminum seal from the vaccine vial. Then remove rubber stopper from vaccine vial and aseptically retain stopper (set aside inverted) for subsequent reuse.

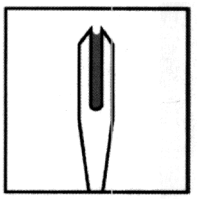
3. The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps muscle is the preferred site for smallpox vaccination. If alcohol is used to clean the site, the skin must be allowed to dry thoroughly to prevent inactivation of the vaccine by the alcohol.

4. Tear off a packette containing a single, sterile bifurcated vaccinating needle.

5. Peel back the packaging approximately halfway exposing the butt-end of needle.

6. Hold butt-end of needle and gently pull bifurcated point end free of packaging.

7 Carefully dip bifurcated end of needle into vaccine. Visually confirm that the needle picks up a drop of vaccine in the space between the two tips.



8. Deposit the drop of vaccine onto clean, DRY site previously prepared for vaccination. ***Do not redip needle into vaccine if needle has touched skin.***

9. With the same needle, and using multiple-puncture technique, vaccinate through drop of vaccine. Holding the bifurcated needle perpendicular to the skin, punctures are rapidly made with strokes vigorous enough to allow a trace of blood to appear after 15-20 seconds. Two or 3 punctures are recommended for primary vaccination; 15 punctures for revaccination.

   Any remaining vaccine should be wiped off with dry sterile gauze and the gauze disposed of in a biohazard waste container.

10. Discard needle in a biohazard waste container.

    Repeat Steps 3 through 10 for each individual to be vaccinated utilizing a new bifurcated needle for each individual vaccinated.

12. If vaccine is to be stored for subsequent use, re-stopper the vial with the rubber stopper and store at 2° to 8°C (36° to 46°F). The vaccine may be stored for no more than 90 days after reconstitution based on viral potency testing.

13. When next needed, remove vial from refrigerator, gently swirl suspension to ensure resuspension, and then carefully take off stopper-cap.

14. Repeat Steps 3 through 10.

15. If vaccine is to be restored for subsequent use, replace stopper-cap and store at 2° to 8°C (36° to 46°F). The vaccine may be stored for no more than 90 days after reconstitution based on viral potency testing.

## Interpretation of Responses:

The vaccination site should be inspected 6 to 8 days after vaccination. Two types of responses have been defined by the World Health Organization (WHO) Expert Committee on Smallpox.[3] They are: 1) major reaction, indicating that virus replication has taken place and vaccination was successful; or 2) equivocal reaction, indicating a possible consequence of immunity capable of suppressing viral multiplication or allergic reactions to an inactive vaccine with production of immunity.

### *Major Reaction*

Major reaction is defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer. The inoculation site becomes reddened and pruritic 3-4 days after vaccination. A vesicle surrounded by a red areola then forms, which becomes umbilicated and then pustular the 7$^{th}$ to 11$^{th}$ day after vaccination, and the pustule begins to dry, the redness subsides, and the lesion usually becomes crusted between the 14$^{th}$ and 21$^{st}$ days. By the end of approximately the third week, the scab falls off, leaving a permanent scar, which at first is pink in color but eventually becomes flesh-colored (see **CLINICAL PHARMACOLOGY**).[2]

Primary vaccination may be accompanied by fever, regional lymphadenopathy, and malaise persisting for a few days.

Revaccination is considered successful if a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion, which may be a scar or ulcer, is present on examination 6-8 days after revaccination.[3] Major reactions, especially when there has been an interval of many years since the last successful vaccination, may be accompanied by fever, regional lymphadenopathy, and malaise persisting for a few days.

### *Equivocal Reaction*

Equivocal reactions are defined as all responses other than major reactions.[3] If an equivocal reaction is observed, vaccination procedures should be checked and vaccination repeated with vaccine from another vial or vaccine lot, if available. If a repeat vaccination by using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult CDC or their state or local health department before giving another vaccination.[2]

## HOW SUPPLIED

Combination package of 1 vial of Dried Smallpox Vaccine, 1 Diluent syringe (0.25 mL), 1 vented needle, 100 individually wrapped bifurcated needles (20 strips, 5 needles per strip). Note: The healthcare provider must have available a sterile 21 gauge or smaller needle to release the vacuum in the vials prior to adding diluent. The needle to release the vacuum is NOT included in the kit.

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## STORAGE

Store un-reconstituted Smallpox Vaccine, Dried, Calf Lymph Type, Dryvax® in the refrigerator (2° to 8°C, 36° to 46°F). DO NOT FREEZE. RECONSTITUTED Dryvax® may be used for 90 days if stored at 2° to 8°C (36° to 46°F), based on viral potency testing, when not in actual use. At time of reconstitution, record date. Dryvax® should not be used after the expiration date regardless of whether it is in the dry or reconstituted form.

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