Report on the Deliberation Results

August 1, 2022

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Brand Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB”
Non-proprietary Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture
Applicant	KM Biologics Co., Ltd.
Date of Application	July 6, 2022

Results of Deliberation

In its meeting held on July 29, 2022, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is not specified.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Review Report

July 21, 2022

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 "KMB"
Non-proprietary Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture
Applicant	KM Biologics Co., Ltd.
Date of Application	July 6, 2022
Dosage Form/Strength	Powder for injection requiring reconstitution before use: Each vial contains at least 2.5×10^7 PFU of live vaccinia virus (LC16m8 strain).
Application Classification	Prescription drug, (4) Drug(s) with a new indication(s)
Items Warranting Special Mention	Expedited review (PSEHB/PED Notification No. 0713-1 dated July 13, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of monkeypox, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition.

Indications

Prevention of smallpox and monkeypox

(Underline denotes additions.)

Dosage and Administration

The vaccine is reconstituted in 0.5 mL of a diluent provided (20 vol% glycerin in water for injection). The reconstituted vaccine is usually administered percutaneously ~~at a dose of 0.01 mL~~ by the multiple puncture technique using a bifurcated needle. ~~The number of punctures is 5 times for primary vaccination and 10 times for other vaccination.~~

(Underline denotes additions, and strikethrough denotes deletions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report

July 21, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 "KMB"
Non-proprietary Name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture
Applicant	KM Biologics Co., Ltd.
Date of Application	July 6, 2022
Dosage Form/Strength	Powder for injection requiring reconstitution before use: Each vial contains at least 2.5×10^7 PFU of live vaccinia virus (LC16m8 strain).
Proposed Indication	Prevention of smallpox and monkeypox (Underline denotes additions.)
Proposed Dosage and Administration	The vaccine is reconstituted in 0.5 mL of a diluent provided (20 vol% glycerin in water for injection). The reconstituted vaccine is usually administered percutaneously ~~at a dose of 0.01 mL~~ by the multiple puncture technique using a bifurcated needle. ~~The number of punctures is 5 times for primary vaccination and 10 times for other vaccination.~~ (Underline denotes additions, and strikethrough denotes deletions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Monkeypox is a disease caused by infection with monkeypox virus (MPXV) that belongs to the Orthopoxvirus genus of the Poxviridae family. The first human monkeypox case was identified in a 9-month-old boy in the Republic of Zaire (currently known as the Democratic Republic of the Congo) in 1970. Since then, human cases have been reported mainly from central and west Africa. In the natural setting, monkeys, rabbits, and rodents including squirrels are known to carry MPXV. Contact with infected animals may result in animal-to-human transmission of MPXV. In addition, human-to-human transmission of MPXV has been also reported. The main routes of transmission of MPXV include contact with skin lesions, body fluid, contaminated objects such as clothing and bedding, and respiratory secretions. After the incubation period usually ranging from 6 to 13 days, monkeypox causes initial symptoms such as fever, intense headache, lymphadenopathy, and myalgia that last 0 to 5 days, followed by appearance of a rash 1 to 3 days after onset of the initial symptoms. The rash tends to be more concentrated on the face and extremities rather than on the trunk, affecting the face (in 95% of cases) and palms of the hands and soles of the feet (in 75% of cases). In addition, not only cornea but also oral mucous membranes (in 70% of cases), genitalia (30%), and conjunctivae (20%) are affected. The rash gradually rise, evolving sequentially into vesicles, pustules, and crusts. Monkeypox is usually a self-limited illness and its symptoms last 2 to 4 weeks, but severe cases may occur in children or is related to the amount of virus exposure. The fatality rate is reported to range from 0% to 11% and tends to be higher, particularly in children (https://www.who.int/news-room/fact-sheets/detail/monkeypox [last accessed on July 18, 2022]). In developed countries, however, no deaths have been reported (https://www.niid.go.jp/niid/ja/kansennohanashi/408-monkeypox-intro.html [last accessed on July 18, 2022]). In addition, MPXV is classified into 2 distinct genetic clades: the central African (Congo Basin) clade and the west African clade. The central African clade is reported to be more transmissible and cause more severe symptoms (https://www.who.int/news-room/fact-sheets/detail/monkeypox [last accessed on July 18, 2022]).

In Japan, monkeypox is designated as a Category IV Infectious Disease under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998). Tabulation of the infection cases was started through the infectious disease surveillance in 2003, and monkeypox cases, including those infected outside of Japan, have yet to be reported in Japan (https://www.niid.go.jp/niid/ja/kansennohanashi/408-monkeypox-intro.html [last accessed on July 18, 2022]). Since May 2022, on the other hand, monkeypox cases in people with no established travel links to monkeypox-endemic countries (mostly in Africa) have been reported in several non-endemic countries such as European countries and the U.S. Most of the cases have been identified in men who have sex with men (MSM). Led by the World Health Organization (WHO), urgent epidemiological studies are currently underway in various countries to develop preventive measures. As of July 4, 2022, 6,027 laboratory confirmed cases of monkeypox have been reported to WHO from 59 countries (https://cdn.who.int/media/docs/default-source/2021-dha-

docs/20220706_monkeypox_external_sitrep_final.pdf?sfvrsn=1b580b3d_4&download=true [last accessed on July 18, 2022]).

Currently available treatment for monkeypox is only palliative care, and no therapeutic agents are approved in Japan. As described below, vaccination against smallpox has been studied as a preventive measure. According to the Smallpox Response Guidelines (Version 5) (https://www.mhlw.go.jp/kinkyu/j-terr/2004/0514-1/dl/01.pdf [last accessed on July 18, 2022]), immunity acquired through exposure to a virus of the Orthopoxvirus genus almost completely responds to the other virus of the same genus (such as smallpox virus, MPXV, and vaccinia virus [strain for smallpox vaccine]), and thus vaccination against smallpox is considered to provide cross-immunity to these viruses. In addition, 5-year epidemiologic data on monkeypox cases reported in the Republic of Zaire from 1980 to 1984 suggested that smallpox vaccination was approximately 85% effective in preventing monkeypox (*Int J Epidemiol.* 1988;17:643-50). Information about the vaccine efficacy reported is available on the website for the situation of monkeypox in Japan provided by the Ministry of Health, Labour and Welfare (MHLW) (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou/kekkaku-kansenshou19/monkeypox_00001.html [last accessed on July 18, 2022]), in the WHO's report of systematic review on changing epidemiology of human monkeypox (*PLoS Negl Trop Dis.* 2022;16:e0010141), in the guidance issued by the Center for Disease Control and Prevention (CDC) (https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html [last accessed on July 18, 2022]), and in the fact sheet issued by the European Centre for Disease Prevention and Control (ECDC) (https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals [last accessed on July 18, 2022]). Furthermore, a report on the genome analysis of MPXV isolates in Europe shows that the MPXV strain prevalent since May 2022 is highly likely to have an origin of the west African clade and is highly homologous to smallpox virus (https://www.biorxiv.org/content/10.1101/2022.06.01.494368v2.full.pdf [last accessed on July 18, 2022]).

The WHO classifies smallpox vaccines developed to date into one of 3 generations. The first-generation vaccines include the Lister strain vaccine and Dryvax (New York City Board of Health [NYCBH] strain) manufactured by Wyeth Laboratories, Inc. These vaccines were manufactured and used during the WHO's Smallpox Eradication Programme and they contributed to the eradication of the disease. The second-generation vaccines are produced using cell culture with a virus strain isolated from the first-generation vaccine strains or their vaccine stocks by a plaque cloning technique, such as ACAM2000 which was derived from plaque purification cloning from Dryvax. The third-generation vaccines include ones prepared in cell culture with an attenuated virus strain developed during the late phase of the Smallpox Eradication Programme, such as LC16m8 strain vaccine and MVA-BN by Bavarian Nordic A/S (brand names outside Japan: JYNNEOS,

Imvanex, and IMVAMUNE) (https://www.who.int/news-room/feature-stories/detail/smallpox-vaccines [last accessed on July 18, 2022]).

Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 "KMB" (hereinafter, smallpox vaccine LC16) is a freeze-dried smallpox vaccine prepared in cell culture, approved for the indication of "prevention of smallpox," and its marketing authorization holder is KM Biologics Co., Ltd. Smallpox vaccine LC16 is manufactured through the process comprising propagation of live vaccinia virus (LC16m8 strain) in the primary rabbit kidney cells, dilution of the obtained viral suspension, formulation of the diluted viral suspension with stabilizers, subdivision of the formulated viral suspension, and lyophilization of the subdivided viral suspension. In the "Vaccines and immunization for monkeypox: Interim guidance" (dated June 14, 2022) developed by the WHO, smallpox vaccine LC16, the third-generation smallpox vaccine, is listed as one of the highly safe smallpox vaccines to be used for prevention of monkeypox (https://www.who.int/publications/i/item/who-mpx-immunization-2022.1 [last accessed on July 18, 2022]). In the WHO's interim guidance, as with smallpox vaccine LC16, MVA-BN approved for prevention of monkeypox in the U.S. and Canada is also listed as one of the third-generation smallpox vaccines to be used in vaccination against monkeypox. MVA-BN was approved in the U.S. in 2019 for "prevention of smallpox and monkeypox in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection" (https://www.fda.gov/media/131802/download [last accessed on July 18, 2022]) based on non-clinical efficacy data (mainly results from a study evaluating vaccine efficacy in the non-human primate [NHP] model) and human immunogenicity data (only data on neutralizing antibody titer against vaccinia virus [Western Reserve strain]). In Canada, MVA-BN was approved in 2020 for "prevention of monkeypox and related orthopoxvirus infection" based on the same study data as those submitted in the U.S. (https://pdf.hres.ca/dpd_pm/00063755.PDF [last accessed on July 18, 2022]).

In view of the above situations in and outside Japan, the applicant has filed an application for partial change approval to extend the indication of smallpox vaccine LC16 to include "prevention of monkeypox" by compiling data supporting the efficacy and safety of smallpox vaccine LC16 in prevention of monkeypox based on the guidelines available in and outside Japan and evidence in published literature. Smallpox vaccine LC16 has not been approved outside Japan. In addition, the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare issued a notification (PSEHB/PED Notification No. 0713-1 dated July 13, 2022, titled "Handling of the review for addition of indication related to monkeypox and granting of expedited review status") to PMDA. Then, the application is required to be handled as one filed in accordance with the notifications issued jointly by the Research and Development Division, Health Policy Bureau and the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare (HPB/RDD Notification No. 4 and PMSB/ELD

Notification No. 104, dated February 1, 1999, titled “Handling of prescription drugs related to off-label use”), and the present application is subject to expedited review.

2. Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for the new indication, no “Data on quality“ have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

For the present application, no evaluation data have been submitted, but published literature of studies on the immunogenicity of smallpox vaccine LC16 and vaccine efficacy have been submitted as reference data on primary pharmacodynamics. The outline of the submitted study data are shown below.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity studies and vaccine efficacy studies

3.1.1.1 Smallpox Vaccine Safety Is Dependent on T Cells and Not B Cells (*J Infect Dis*. 2011;203:1043-53)

Cynomolgus monkeys (unknown sex) percutaneously received a single dose of 2.5×10^5 PFU/animal of smallpox vaccine LC16 (n = 14), 2.5×10^5 PFU/animal of Dryvax (n = 4), or phosphate-buffered saline (PBS) (n = 6) with a bifurcated needle. The animals were intravenously challenged with 5×10^7 PFU of MPXV (Zaire 79 strain) 60 days after vaccination.

During a period from vaccination to challenge with MPXV, smallpox vaccine LC16 and Dryvax induced comparable neutralizing antibody and cell-mediated immune responses to MPXV.

In the negative control group, intravenous infection with MPXV resulted in multiple skin lesions throughout the body followed by deaths or euthanization in all the animals within 12 days after challenge with MPXV. The number of skin lesions in smallpox vaccine LC16-immunized animals was greater than that in Dryvax-immunized animals, but was smaller than that in animals in the negative control group. In addition, in smallpox vaccine LC16-immunized animals and Dryvax-immunized animals, crusts formed until 12 days after challenge with MPXV, and no deaths occurred. The blood viral genome loads in the smallpox vaccine LC16 group and Dryvax group were remarkably lower than that in the negative control group and became undetectable by 9 days after challenge with MPXV.

3.1.1.2 LC16m8, a Highly Attenuated Vaccinia Virus Vaccine Lacking Expression of the Membrane Protein B5R, Protects Monkeys from Monkeypox (*J Virol*. 2006;80:5179-88)

Cynomolgus monkeys percutaneously received a single dose of at least 1×10^8 PFU/mL of smallpox vaccine LC16 (3 females per group), at least 1×10^8 PFU/mL of Lister strain vaccine (2 or 3 females per group), or a mock-up vaccine as negative control (2 females or 1 male and female each per group) with a bifurcated needle. Five weeks after vaccination, smallpox vaccine LC16-immunized animals, Lister strain vaccine-immunized animals, and mock-immunized animals were intranasally inoculated with 1×10^6 PFU of MPXV Liberia strain or subcutaneously inoculated with 1×10^6 PFU of Zr-599 strain.

During a period from vaccination to challenge with MPXV, smallpox vaccine LC16 and Lister strain vaccine induced anti-vaccinia virus IgG antibodies and neutralizing antibody responses to MPXV.

After the intranasal inoculation with MPXV, viremia occurred in the negative control group but did not occur in the smallpox vaccine LC16 group or Lister group. At clinical observation after challenge with MPXV, papulovesicles and rhinorrhoea were observed in the negative control group, but no monkeypox-related lesions were observed in the smallpox vaccine LC16 group or Lister group. At histopathological examination 3 weeks after challenge with MPXV, lesions in the skin, lungs, pancreas, thymus, tonsil, and lymph nodes were observed in the negative control group, but no monkeypox-related lesions were observed in the smallpox vaccine LC16 group or Lister group.

After the subcutaneous inoculation with MPXV, the blood viral genome load in the smallpox vaccine LC16 group was higher than that in the Lister group but was lower than that in the negative control group, with a shorter period of detection. At clinical observation after challenge with MPXV, many severe monkeypox-related lesions such as populovesicles were observed in mock-immunized animals, and thus these animals were euthanized. In the smallpox vaccine LC16 group, on the other hand, lesions limited to the site of MPXV inoculation (erythema, populovesicles, and ulcer) were observed. In the Lister group, no monkeypox-related lesions were observed. At histopathological examination 3 weeks after exposure to MPXV, monkeypox-related lesions in the lymph nodes, thymus, tonsil, lungs, trachea, stomach, small intestine, colon, rectum, liver, bladder, uterus, ovaries, and skins were observed in the negative control group, but no monkeypox-related lesions were observed in the smallpox vaccine LC16 group except for skin lesions at the site of MPXV inoculation. In the Lister group, no monkeypox-related lesions were observed.

3.1.1.3 A Single Vaccination of Nonhuman Primates with Highly Attenuated Smallpox Vaccine, LC16m8, Provides Long-term Protection against Monkeypox (*Jpn J Infect Dis*. 2017;70:408-15)

Cynomolgus monkeys percutaneously received a single dose of at least 1×10^8 PFU/mL of smallpox vaccine LC16 (3 males per group), at least 1×10^8 PFU/mL of Lister strain vaccine (2 males per group), or a mock-up vaccine as negative control (3 males and 1 female per group) with a bifurcated needle. Smallpox vaccine LC16-

immunized animals, Lister strain vaccine-immunized animals, and mock-immunized animals were subcutaneously inoculated with 10^6 PFU of MPXV (Zr-599 strain) 6 or 12 months after vaccination.

During a period from vaccination to challenge with MPXV, smallpox vaccine LC16 and Lister strain vaccine induced anti-vaccinia virus IgG antibodies. The anti-vaccinia virus IgG antibody titer in smallpox vaccine LC16-immunized animals was lower than that in Lister strain vaccine-immunized animals 6 and 12 months after vaccination, but increased immediately after challenge with MPXV.

After challenge with MPXV, several papulovesicular lesions, as well as ulcerative lesions at the site of MPXV inoculation were observed in the negative control group. In the smallpox vaccine LC16 group, on the other hand, only ulcerative lesions at the site of MPXV inoculation were observed. None of such skin lesions were observed in the Lister group. At histopathological examination 3 weeks after challenge with MPXV, monkeypox-related lesions were observed in many organs of the lymphatic, respiratory, gastrointestinal, and urogenital systems in mock-immunized animals, but none of such lesions were observed in the smallpox vaccine LC16 group or Lister group.

3.R Outline of the review conducted by PMDA

The active ingredient of smallpox vaccine LC16 is vaccinia virus (LC16m8 strain). Smallpox vaccine LC16 induces cross-immunity to smallpox virus, thereby preventing smallpox. This is the same as the mechanism by which smallpox vaccine LC16 acts to prevent monkeypox. Smallpox vaccine LC16 is considered to induce cross-immunity (humoral and cell-mediated immune responses) to MPXV, which belongs to the Orthopoxvirus genus as with vaccinia virus, thereby inhibiting MPXV replication and preventing monkeypox. The immunogenicity and challenge studies in monkeys showed that smallpox vaccine LC16 was immunogenic against MPXV (induction of neutralizing antibodies and cell-medicated immune response), prevented viremia after MPXV infection, and prevented the onset of monkeypox-related lesions, although its effects tended to be weaker than those of the first-generation smallpox vaccines such as Lister strain vaccine and Dryvax. Based on the above study results and from a pharmacological viewpoint, PMDA considers it reasonable to expect smallpox vaccine LC16 to induce cross-immunity to MPXV and thereby prevent monkeypox in humans as well.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

No applicable studies have been conducted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for the new indication, no additional study results have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

No applicable studies have been conducted.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

PMDA reviewed published literature and reports from public research projects that became publicly available after the approval of smallpox vaccine LC16 because the data served to evaluate the efficacy and safety of smallpox vaccine LC16.

7.1 Foreign phase I/II study

7.1.1 Safety and immunogenicity of LC16m8, an attenuated smallpox vaccine in vaccinia-naive adults (*J Infect Dis.* 2011;204:1395-402)

A randomized double-blind comparative study was conducted in healthy adults aged 18 to 34 years without prior smallpox vaccination in the U.S. in 2004 and 2005, to evaluate the safety of smallpox vaccine LC16 versus Dryvax and compare the neutralizing antibody titers against viruses of the Orthopoxvirus genus including MPXV 30 days after vaccination (Day 30). A single dose of either vaccine 0.02 μL (1×10^8 PFU/mL) was administered percutaneously (through 15 punctures) with a bifurcated needle.

A total of 125 subjects (81 men and 44 women) received smallpox vaccine LC16, and all showed a "take (major cutaneous reaction)"[1)] at the administration site between Days 6 and 12. In 26 subjects randomly extracted from those receiving smallpox vaccine LC16, the geometric mean titer (GMT) of neutralizing antibodies against MPXV on Day 30 was 112 (95% confidence interval [CI], 82-307). This shows that smallpox vaccine LC16 induced neutralizing antibodies against not only various strains of vaccinia virus (NYCBH, Lister, and LC16m8 strains) but also MPXV.

As for the safety, 82% (102 of 125) of subjects receiving smallpox vaccine LC16 experienced at least 1 local reactogenicity event, and the incidence of local reactogenicity events was as follows: feeling hot, 36% (45 of 125); vaccination site tenderness, 42% (52 of 125); limited arm movement, 12% (15 of 125); axillary lymphadenopathy, 37% (46 of 125); axillary lymph node tenderness, 48% (60 of 125); rash, 2% (3 of 125);

[1)] A clear skin lesion at the administration site that indicates successful acquisition of immunity.

satellite lesions,[2)] 2% (3 of 125). Systemic reactogenicity events including pyrexia occurred in 74% of the subjects receiving smallpox vaccine LC16. No subjects experienced serious adverse events related to the vaccination, such as postvaccinal encephalitis/encephalopathy, dermal complication, and myocarditis/pericarditis.

7.2 Japanese phase IV study

7.2.1 Freeze-dried live attenuated smallpox vaccine prepared in cell culture LC16-KAKETSUKEN (*Vaccine.* 2015;33:6120-7)

A use-results survey was conducted to evaluate the safety of smallpox vaccine LC16 in 268 members of Japan Self-Defense Force who were aged 19 to 52 years (261 men and 7 women) at a single center in Japan from 2005 to 2010. A single dose of smallpox vaccine LC16 at 0.01 mL (at least 1×10^8 PFU/mL) was administered percutaneously with a bifurcated needle. The number of punctures was 5 times in primary vaccinees (without prior smallpox vaccination) and 10 times in previously vaccinated individuals.

A "take" was observed[3] in 94.4% (185 of 196) of the primary vaccinees and 81.7% (58 of 71) of the previously vaccinated individuals.

A total of 268 individuals received smallpox vaccine LC16. Adverse events occurred in 27.0% (53 of 196) of the primary vaccinees, 5.6% (4 of 71) of the previously vaccinated individuals, and 100% (1 of 1) of the individual with unknown vaccination history. The following adverse events were observed in this survey: axillary lymphadenopathy in 52 individuals (19.4%), pyrexia in 4 (1.5%), malaise in 2 (0.7%), rash in 1 (0.4%), vaccination site erythema in 14 (5.2%), vaccination site swelling in 1 (0.4%), and autoinoculation in 1 (0.4%). All of them were non-serious. Dermal complication associated with vaccination occurred in 2 primary vaccinees: one experienced dermatitis allergic but not eczema vaccinatum (outcome, resolved), and the other experienced rash unrelated to vaccination. Electrocardiography revealed mild atrioventricular block first degree in 2 individuals, but both events were considered unrelated to vaccination. After vaccination, laboratory test abnormal was observed in several individuals, but all events were considered unrelated to vaccination. No individuals died or had serious adverse events (e.g., cardiovascular diseases, encephalitis, satellite lesions, and progressive vaccinia) during the survey period.

[2)] Blisters or pustules observed near the administration site.
[3)] The article does not mention the outcome of the 1 individual with unknown vaccination history.

7.3 Clinical research

7.3.1 Clinical and Immunological Response to Attenuated Tissue-Cultured Smallpox Vaccine LC16m8 (*JAMA*. 2009;301:1025-33)

Clinical research was conducted to evaluate the safety of smallpox vaccine LC16 in healthy members of Japan Self-Defense Force who were aged 18 to 55 years with no skin lesions at a single center from 2002 to 2005. A single dose of smallpox vaccine LC16 at approximately 4 μL (at least 1×10^8 PFU/mL) was administered percutaneously with a bifurcated needle. The number of punctures was 5 times in primary vaccinees (without prior smallpox vaccination) and 10 times in previously vaccinated participants. Of the 3,468 participants enrolled, 3,221 (92.8%) were vaccinated. Of the 3,221 vaccinated participants, 1,529 (47.5%) were primary vaccinees and 3,168 (98.4%) were men.

A "take" was observed in 94.4% (95% CI, 93.2%-95.9%) (1,443 of 1,529) of the primary vaccinees and 86.6% (95% CI, 85.0%-88.2%) (1,465 of 1,692) of the previously vaccinated participants.

No serious adverse events (e.g., autoinoculation/inoculation by exposure to vaccinated person, eczema vaccinatum, progressive vaccinia, generalised vaccinia, encephalitis, and symptomatic myocarditis) were reported during the follow-up period of 10 to 14 days after administration of smallpox vaccine LC16. Adverse events occurred in 4 participants within 30 days after vaccination, and the events in 2 of them were suspected to be severe. One of the 2 participants was a male primary vaccinee aged 26 years. He experienced rash 3 days after vaccination (Day 3), which spread from the extremities to the trunk, resulting in hospitalization on Day 20. The rash was diagnosed as dermatitis allergic, and its causal relationship to vaccination was not ruled out. The other participant was a male primary vaccinee aged 29 years. He experienced rash on the trunk on Day 10 and was given a diagnosis of erythema multiforme.

Neither electrocardiogram abnormal nor symptoms of heart disorders were reported during the administration of smallpox vaccine LC16. Serum troponin T was measured in 347 participants to confirm whether they had asymptomatic myocarditis. In all of them, serum troponin T levels measured before and after vaccination were below the detection limit (0.01 ng/mL). Medical records of 1,066 participants (491 primary vaccinees and 575 previously vaccinated participants) were surveyed retrospectively for mild adverse events. The survey identified 148 adverse events; the most common event was axillary lymphadenopathy, accounting for 65% (96 events) of the identified events (Table 1).

Table 1 List of adverse events

	Primary vaccinees (N = 491) n (%)	Previously vaccinated participants (N = 575) n (%)
Axillary lymphadenopathy	76 (15.5)	20 (3.5)
Low grade fever (>37.5°C)	13 (2.6)	8 (1.4)
Skin pruritus/urticaria	4 (0.8)	3 (0.5)
Flu like symptoms	5 (1.0)	1 (0.2)
Headache	5 (1.0)	0 (0.0)
Myalgia (upper arm, chest, and neck)	3 (0.6)	1 (0.2)
Cervical lymphadenopathy	2 (0.4)	1 (0.2)
Diarrhoea	1 (0.1)	1 (0.2)
Acute deafness neurosensory	1 (0.2)	0 (0.0)
Giddiness	0 (0.0)	1 (0.2)
Eye socket swelling	0 (0.0)	1 (0.2)
Arthritis	0 (0.0)	1 (0.2)

N = number of participants surveyed; n = number of events identified

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

In the phase I/II study conducted in healthy adults without prior smallpox vaccination in the U.S., a single dose of smallpox vaccine LC16 induced a neutralizing antibody response against MPXV. Smallpox vaccine LC16 was thus shown to induce a neutralizing antibody response against not only various strains of vaccinia virus (NYCBH, Lister, and LC16m8 strains) but also other viruses of the Orthopoxvirus genus [see Section 7.1.1]. In previously vaccinated individuals as well, smallpox vaccine LC16 induced a neutralizing antibody response against MPXV[4] (https://mhlw-grants.niph.go.jp/project/26727 [last accessed on July 18, 2022]).

In the clinical research conducted in members of Japan Self-Defense Force, 1,529 adults without prior smallpox vaccination received the primary dose of smallpox vaccine LC16 between 2002 and 2005 in Japan. The results showed that 94.4% (1,443 of 1,529) of them had a "take" indicating successful immunization [see Section 7.3.1]. The clinical studies conducted in the U.S. and Japan showed no marked differences in (a) the proportion of vaccinees with a "take" or (b) induction of a neutralizing antibody response against vaccinia virus.

PMDA's view:

Smallpox vaccine LC16 containing vaccinia virus (LC16m8) as the active ingredient induces cross-immunity between smallpox and monkeypox and its immunogenicity is not considered to be affected significantly by ethnic differences. Smallpox vaccine LC16 probably prevents the onset of monkeypox in the Japanese population, because (a) the vaccine induces a neutralizing antibody response against MPXV in the Japanese population and (b) in the non-clinical studies, the vaccine induced a neutralizing antibody response against MPXV through cross-immunity and showed a preventive effect against monkeypox.

[4] According to the report, the neutralizing antibody titer measured after administration of the positive control was approximately 10 times lower than expected; this resulted in lack of data for accurate evaluation of neutralizing antibody response.

7.R.2 Safety

According to a WHO report, smallpox vaccines used before the development of smallpox vaccine LC16 caused various adverse reactions (https://apps.who.int/iris/handle/10665/337041 [last accessed on July 18, 2022]). Smallpox vaccine LC16, on the other hand, was administered to approximately 50,000 children in 1973 and 1974 by the National Smallpox Vaccination Research Committee (nationwide research network for understanding health hazards related to smallpox vaccination and selection or development of vaccines with less adverse reactions), and no problematic adverse reactions were reported. Of these children, 10,578 were subjected to detailed clinical observation. Among them, 9,538 were vaccinated in 1974, with 95.1% (9,075 of 9,538) having a "take." Of the 9,075 children, 8,544 were observed for at least 14 days. Of the 8,544 children, 7.8% (663) experienced pyrexia of ≥37.5°C between 4 and 14 days after vaccination. In 85% of those with pyrexia, fever persisted for ≤2 days (*Clinical virology*. 1975;3:269-79). Furthermore, an electroencephalography study for central nervous system complications raised no relevant concerns (*Clinical virology*. 1975;3:269-79, *Japanese journal of pediatrics*. 1976;29:1409-12).

In the foreign phase I/II study in healthy adults without prior smallpox vaccination conducted in the U.S., no serious adverse events (e.g., postvaccinal encephalitis/encephalopathy, dermal complication, and myocarditis/pericarditis) occurred [see Section 7.1.1]. In Japan, through a smallpox vaccination program initiated in 2002 as a crisis management measure, smallpox vaccine LC16 has been administered to the limited population (mainly healthy adults belonging to Japan Self-Defense Force). According to the reports from (a) the clinical research in 3,221 participants who received smallpox vaccine LC16 between 2002 and 2005 (1,529 primary vaccinees and 1,692 previously vaccinated individuals) and (b) the use-results survey on smallpox vaccine LC16 from 2005 to 2010, no serious adverse events occurred, such as postvaccinal encephalitis/encephalopathy and dermal complications (problematic events with traditional vaccine strains including the Lister strain) or myocarditis/pericarditis (problematic events with the NYCBH strain used in Dryvax etc. in the U.S.); further, the incidences of local adverse reactions at the administration site and systemic adverse reactions (e.g., pyrexia and headache) were similar to those reported by the survey of the National Smallpox Vaccination Research Committee conducted in children in 1973 and 1974 [see Sections 7.1.1 and 7.3.1]. However, the clinical research (*JAMA*. 2009;301:1025-33) reported severe cutaneous symptoms for which a causal relationship to smallpox vaccine LC16 could not be ruled out (dermatitis allergic and erythema multiforme in 1 participant each). As for post-vaccination transmission of live vaccinia virus strains, the use-results survey of smallpox vaccine LC16 identified autoinoculation in 1 vaccinee after the market launch. The event was mild in severity with unknown transmitted site.

In order to raise caution, confirmed pregnant women are classified as “persons ineligible for vaccination” in the package insert for smallpox vaccine LC16. No data are available on the effect of vaccination in women of childbearing potential. The safety of smallpox vaccine LC16 has not been established in children born to women who received smallpox vaccine LC16 before being pregnant or in children breastfed by women who received the vaccine. As with other live vaccines, the “Precautions Concerning Vaccination” section of the package insert for smallpox vaccine LC16 will include precautionary statements about (a) contraception in women of childbearing potential before and after vaccination and (b) use in breast-feeding women.

PMDA’s view:

Based on the reported literature, the safety profile of smallpox vaccine LC16 remains unchanged by the addition of the new indication “prevention of monkeypox,” and the safety in humans including children is acceptable. However, since severe cutaneous symptoms (dermatitis allergic and erythema multiforme) were reported after the launch of smallpox vaccine LC16, these symptoms should be classified as an important potential risk. Attention should be paid to information regarding the cutaneous symptoms that may be accumulated in the future, and actions should be taken as necessary. Autoinoculation after administration of smallpox vaccine LC16 was reported only in 1 vaccinee, but it is an important potential risk associated with the vaccine. Information regarding autoinoculation should therefore be disseminated through not only the package insert but also materials for healthcare professionals and vaccinees, to ensure full understanding about autoinoculation through explanations and instructions. PMDA accepts the applicant’s proposal to include precautionary statements in the package insert regarding (a) contraception in women of childbearing potential before and after vaccination and (b) use in breast-feeding women, as with other live vaccines.

7.R.3 Clinical positioning

PMDA’s view:

The “Vaccines and immunization for monkeypox: Interim guidance” developed by the WHO (https://www.who.int/publications/i/item/who-mpx-immunization-2022.1 [last accessed on July 18, 2022]) supports the clinical usefulness of smallpox vaccines in prevention of monkeypox. In the guidance, smallpox vaccine LC16 is listed as one of the smallpox vaccines to be used for prevention of monkeypox. Globally, smallpox vaccine LC16 is the only smallpox vaccine that can be administered to children and is positioned as the suitable vaccine that should be used based on the benefit-risk balance in people who are at risk of adverse reactions to vaccination but need to be vaccinated.

In Japan, smallpox vaccines had been administered to children at birth, before elementary school admission, and before elementary school graduation until 1976, when smallpox vaccination was removed from the routine vaccination program. As for the efficacy of vaccination in previously vaccinated individuals, the vaccine titer

required to provide a "take" is higher in individuals who received a traditional vaccine produced on cow skin as the primary dose ≥20 years ago, than in primary vaccinees (*Bulletin of the Public Health Laboratory of Chiba Prefecture*. 2004;28:11-4). Smallpox vaccine LC16 provided a successful "take" to both people with and without prior smallpox vaccination (*JAMA.* 2009;301:1025-33) and induced a neutralizing antibody response against MPXV (https://mhlw-grants.niph.go.jp/project/26727 [last accessed on July 18, 2022]).

Based on the above, smallpox vaccine LC16 is expected to be clinically useful in preventing monkeypox in people with prior smallpox vaccination as well as those without.

7.R.4 Indications

No clinical studies of smallpox vaccine LC16 have been conducted to evaluate its preventive effect against monkeypox. PMDA, however, considers that the proposed indication "Prevention of smallpox and monkeypox" (Underline denotes additions.)" is reasonable for the following reasons:

(a) The non-clinical pharmacology studies of smallpox vaccine LC16 showed its preventive effect against monkeypox.
(b) There are similarities between smallpox virus and MPXV.
(c) Smallpox vaccine LC16 induced a neutralizing antibody response against various viruses of the Orthopoxvirus genus in humans.
(d) Traditional smallpox vaccines prevent the onset of smallpox.

7.R.5 Dosage and administration

The applicant's explanation about modification of the dosage and administration:
The dosage and administration before the present application was as follows:

> "The vaccine is reconstituted in 0.5 mL of a diluent provided (20 vol% glycerin in water for injection). The reconstituted vaccine is administered percutaneously at a dose of 0.01 mL by the multiple puncture technique. The number of punctures is 5 times for primary vaccination and 10 times for other vaccination."

The safety and efficacy of smallpox vaccine LC16 administered through 15 punctures, a number not included in the above dosage and administration, were confirmed in the foreign phase I/II study in healthy adults without prior smallpox vaccination in the U.S. (*J Infect Dis.* 2011; 204: 1395-402). The applicant thus proposed a modified dosage and administration for the present application, in accordance with the Smallpox Response Guidelines (Version 5) (https://www.mhlw.go.jp/kinkyu/j-terr/2004/0514-1/dl/01.pdf [last accessed on July 18, 2022]) and Instructions for Smallpox Vaccination with Bifurcated Needle, issued by WHO (https://apps.who.int/iris/handle/10665/67962 [last accessed on July 18, 2022]). In the proposed dosage and administration statement, the phrase specifying the vaccine volume to be withdrawn is deleted because the package insert for the smallpox vaccination needle used in Japan does not specify the volume that can be

withdrawn with the needle, and because multiple puncture technique does not require accurate withdrawal of a specified volume.

PMDA's view:

In the foreign phase I/II study, vaccination using a bifurcated needle induced a neutralizing antibody response against MPXV. In view of this result and the WHO's instructions for smallpox vaccination, the following dosage and administration statement proposed by the applicant is appropriate:

> "The vaccine is reconstituted in 0.5 mL of a diluent provided (20 vol% glycerin in water for injection). The reconstituted vaccine is usually administered percutaneously by the multiple puncture technique using a bifurcated needle."

As for instructions for vaccine administration by the multiple puncture technique, it is acceptable to delete the volume to be withdrawn from the dosage and administration statement, and to specify the number of punctures in the "Precautions Concerning Vaccine Administration" section of the package insert.

7.R.6 Post-marketing investigations

The applicant's explanation:

At the present, the new indication "prevention of monkeypox" does not necessitate additional studies or surveillance to collect evidence or information about the clinical use of smallpox vaccine LC16 in and outside Japan, for the following reasons:

(a) The new indication "prevention of monkeypox" is not considered to change the safety profile of smallpox vaccine LC16.
(b) The marketing authorization of smallpox vaccine LC16 was transferred to the applicant in 2002. Since then, there have been no reported events that raised concerns about the safety of the vaccine.
(c) After the approval of the new indication, smallpox vaccine LC16 is supposed to be used in a limited manner as has been done under the supervision of MHLW, in accordance with the Japanese government's policy such as the Smallpox Response Guidelines (Version 5) (https://www.mhlw.go.jp/kinkyu/j-terr/2004/0514-1/dl/01.pdf [last accessed on July 18, 2022]).

PMDA's view:

The safety data regarding smallpox vaccine LC16 used to prevent monkeypox in clinical practice should be collected at the current scientific level, for the following reasons:

(a) Human experience with smallpox vaccine LC16 is limited.
(b) The characteristics of vaccinees for prevention of monkeypox are different from those for prevention of smallpox, the approved indication.
(c) The medical environment is different from when smallpox vaccine LC16 was initially approved.

The efficacy and safety data of smallpox vaccine LC16 in prevention of monkeypox should therefore be collected in a systematic manner. Smallpox vaccine LC16 is administered by a special method using a bifurcated needle, but this administration method has not been used in the routine vaccination program since 1976 and is therefore unfamiliar to most healthcare professionals. Thus, healthcare professionals should be appropriately informed about (a) the reconstitution and administration methods of smallpox vaccine LC16, (b) health management instructions that should be given to individuals who have received the vaccine, and (c) disposal and control of the reconstituted vaccine. As described in Section 7.R.2, individuals who are to receive smallpox vaccine LC16 should be adequately informed and cautioned so that they understand precautions necessary for receiving the vaccine.

PMDA asked the applicant to discuss whether post-marketing surveillance should be conducted as a part of additional pharmacovigilance activities to investigate the safety specification of smallpox vaccine LC16.

The applicant's explanation about the necessity of the post-marketing surveillance:
The following concerns associated with smallpox vaccine LC16 should be investigated: shock, anaphylaxis, severe cutaneous symptoms, autoinoculation (heterotopic inoculation), and horizontal transmission. Because post-vaccination information should be collected from vaccinees to investigate these events, the applicant will collect information as much as possible as a part of pharmacovigilance activities and will collect data through a general use-results survey. Since smallpox vaccine LC16 is supposed to be used in a limited manner in accordance with the government's vaccination policy, the applicant will plan the general use-results survey based on the government's vaccination policy.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for smallpox vaccine LC16 should include the safety specification presented in Table 2, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 3.

Table 2 Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Seizure, febrile seizure	• Severe cutaneous symptoms • Shock, anaphylaxis • Autoinoculation (ectopic inoculation), horizontal transmission	None
Efficacy specification		
None		

Table 3 Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (prevention of monkeypox) • General use-results survey	• Disseminate data gathered during early post-marketing phase vigilance (prevention of monkeypox) • Organize and disseminate information materials for healthcare professionals • Organize and disseminate information materials for vaccinees

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

In the present application, no data subject to compliance assessment have been submitted, and thus the concerned assessment is not conducted.

9. Overall Evaluation

Smallpox vaccine LC16 is expected to be effective in preventing monkeypox based on data including (a) the evidence for its efficacy in preventing monkeypox shown by the published literature submitted and (b) its clinical usefulness supported by the WHO's guidance. In addition, the safety profile of smallpox vaccine LC16 remains unchanged by the addition of the new indication "prevention of monkeypox," and the safety data in the published literature dose not raise particular concerns about its safety.

There are no monkeypox vaccines in the world that have been evaluated for efficacy in clinical studies. In response to current global outbreak of monkeypox, the WHO issued a statement to the effect that public health measures such as vaccination should be taken in each country. In view of this situation and the benefits of smallpox vaccine LC16, PMDA has concluded that smallpox vaccine LC16 may be approved for the indications and dosage and administration shown below, with the following approval condition.

Indications

Prevention of smallpox and monkeypox

(Underline denotes additions.)

Dosage and Administration

The vaccine is reconstituted in 0.5 mL of a diluent provided (20 vol% glycerin in water for injection). The reconstituted vaccine is usually administered percutaneously ~~at a dose of 0.01 mL~~ by the multiple puncture technique using a bifurcated needle. ~~The number of punctures is 5 times for primary vaccination and 10 times for other vaccination.~~

(Underline denotes additions, and strikethrough denotes deletions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

CDC	Center for Disease Control and Prevention
CI	Confidence Interval
ECDC	European Centre for Disease Prevention and Control
FDA	U.S. Food and Drug Administration
IgG	Immunoglobulin G
MPXV	Monkeypox virus
MSM	Men who have sex with men
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NHP	Non-Human Primate
PFU	Pock Forming Unit or Plaque Forming Unit
PBS	Phosphate-Buffered Saline
WHO	World Health Organization
PMDA	Pharmaceuticals and Medical Devices Agency
Smallpox vaccine LC16	Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB”: A smallpox vaccine containing the vaccinia virus LC16m8 strain as the active ingredient.