Abstract

The COVID-19 Vaccine BIBP, also known as Inactivated COVID-19 (VERO CELL) vaccine is produced in Vero Cells and inactivated with β-propiolactone. The SARS-CoV-2 antigen is purified and adsorbed with Aluminum Hydroxide. The product can be stored at 2-8°C for 24 months and holds a VVM7. The applicant, the Beijing Institute of Biological Products Co., Ltd. (BIBP) (China) had submitted a dossier in CTD format to support the Emergency Use Listing (EUL).

The vaccine has been authorized by the Chinese National Regulatory Authority (NRA) – the National Medicinal Product Administration (NMPA) - as well as other regulatory authorities.

The assessment included the review of the quality, non-clinical, clinical - including Risk Management Plan (RMP) - and inspection of the manufacturing facilities.

The application included interim analyses of a phase1/2 and a bridging study conducted in China, and a phase 3 study conducted in the United Arab Emirates and other Arab countries. Vaccine efficacy against laboratory-confirmed symptomatic COVID-19 was estimated to be 78% in adults 18-59 years of age. Lack of data prevented estimating the efficacy of the vaccine in individuals 60 years of age and older and with comorbidities. The vaccine was shown to be immunogenic and no safety concerns have been identified in clinical studies.

The majority of the deficiencies found during the assessment process were resolved.

This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).

1 Introduction

1.1 Background

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.
On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization’s Geneva headquarters on 11–12 February 2020\(^1\) to assess what is known about the new severe acute respiratory coronavirus-2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint\(^2\) aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

### 1.2 COVID-19 vaccines

Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its native conformation) was identified as the immunodominant antigen of the virus\(^3\). Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease\(^4\).

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit-risk approach.

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\(^2\) [https://apps.who.int/blueprint-brochure/](https://apps.who.int/blueprint-brochure/)


The information available on COVID-19 candidate vaccines and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g. MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials.

During the past year, there was an unprecedented global effort to develop safe and effective vaccines against COVID-19. These vaccines represent some of the most important tools in ending the pandemic, when combined with proven public health and social measures. Very encouraging results on the safety and efficacy of candidate vaccines have been reported for several candidates. However, the current epidemiological scenario is becoming increasingly complicated with the surge of virus variants due to mutations associated with increased viral transmission and in some cases neutralizing antibody escape. These variants of concern make effective changes in the virus’s ‘Spike’ protein, which the virus uses to enter human cells and some of these variants are posing real challenges for vaccine’s efficacy.

In this complex scenario, vaccines that could exert protective immunity after a single dose are preferred.

**1.2.1 The Inactivated SARS-COV-2 (Vero Cell) vaccine**

The product is a semi-transparent suspension with slight white color, which could be layered due to precipitation, which can be easily dispersed by shaking. The product is formulated from inactivated SARS-CoV-2 antigen, PBS solution and aluminum hydroxide to form the liquid vaccine. The antigen is obtained from SARS-CoV-2 strain, which is inoculated on Vero cells for culturing, virus harvesting, β-propiolactone inactivation, concentration and purification, ultrafiltration and sterile filtration. Adsorption on aluminum adjuvant takes place during final bulk formulation.

The virus strain used to produce COVID-19 vaccine BIBP, was selected after cell adaptive culture screening and cross-protection evaluation (derived from clinical isolates from Chinese CDC in January 2020). Vero cells were used as cell substrates. The presentation is 1ml pre-filled syringes (PFS) with 0.5 ml/ syringe. A 2ml vial presentation containing 0.5 ml of vaccine is also available. Both presentations are monodose.

Immunization schedule: 2 doses of COVID-19 vaccine BIBP are inoculated to the deltoid muscle of the upper arm according to the immunization schedule at an interval of 21-28 days (D0 & D21 +7 days). Each dose contains 0.5mL of COVID-19 vaccine. The booster immunization for this product has not been determined.

**1.3 Emergency Use Listing**

The Emergency Use Listing (EUL) is a time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the manufacturer

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5 [https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines](https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)
is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO’s recommendation for its use following a thorough scientific risk benefit assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under EUL within their country.

2 Assessment process

COVID-19 vaccine BIBP was assessed under the WHO EUL procedure based on the review of data on quality, safety, efficacy, risk management plan (RMP) and programmatic suitability performed by WHO Vaccine Prequalification experts and evaluators from national regulatory authorities (NRAs) from different countries and regions. Emphasis was placed on the risk-benefit of the vaccine and therefore on the RMP because of the need to consider the perspectives and concerns of regulators from different regions, that might otherwise not be considered by the NRA of reference for WHO. This assessment is expected to be focused on issues related to its own jurisdiction and reflect the needs from the regions. In addition, an international inspection team of experts from WHO, South Africa and observers from the NMPA of China performed a good manufacturing (GMP) inspection.

The NRA of reference for WHO for this submission is the NMPA. The information package submitted to WHO followed the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD).

3 Scientific Review

3.1 Quality overview

From the very early stages of product development, the company opted for inactivation technology to manufacture their COVID-19 vaccine for the following reasons:

1. this methodology has been used for decades and the resulting vaccines have been proven safe and efficacious;
2. BIBP has already established a reliable vaccine inactivation process platform for sIPV vaccine, which had been approved and marketed for years.
3. virus strains could easily be obtained in China at the beginning of the product development, in January 2020.

Drug Substance

Manufacture, control of materials and drug substance

The Drug Substance (DS) is manufactured in a built for purpose level 3 biosafety laboratory following a conventional pathway as follows:

- cell culture of Vero cells during 3 passages before transferring in 300L bioreactor for 2 passage;
- inoculation and harvesting for 48 to 96 hours and subsequent filtering for clarification;
• β-propiolactone inactivation for 20-24 hours followed by thermal hydrolysis of inactivation agent;
• 300 kD membrane ultrafiltration for concentration, removal of cellular DNA for purification, 100 kD membrane ultrafiltration and final sterile filtration.

Vero master cell bank at passage level 139 and working cell bank at passage level 142 were obtained from Health Protection Agency Culture Collection (UK) at passage level 134. All controls are performed by the Chinese National Institute for Food and Drug Control (WHO collaborative centre), as well as controls on end of production cells. This was found acceptable.

Virus seed banks were established from an Original Virus Seed (OVS), BJ-P4. This OVS was passaged 3 times from 19nCOV-CDC-TAN-HB02 strain (or BJ-P1). This strain was obtained by Chinese CDC from a throat swab sample from the patient (donor) which was propagated on Vero cells for up to 7 passages for virus isolation and purification. Characterisation of HB02 strain by detailing position on Nextstrain tree and mutational profile in comparison with original swab was also provided. Controls of master and working viral seeds were performed by BIBP.

Raw materials are controlled in house according to national and international compendium and all measures to avoid contamination with biological agents like Transmissible Spongiform Encephalopathy (TSE)/Bovine Spongiform Encephalopathy (BSE) are taken.

DS is controlled in house by validated/verified methods derived from Ph.Eur., CP or developed in-house. The references used to control DS are developed either in house or purchased.

Container Closure System
Details on the containers for Vero cell, virus seeds, inactivated intermediate and bulk were provided. Studies on leachable/extractable for the bulk container (study performed by manufacturer of container or product specific study) are still to be provided. However, this has a minor impact on overall quality of the finished product, this could be followed up post recommendation.

Stability
The following studies have been planned on bulk:
• up to 24 months at 2-8°C (long term, still ongoing);
• up to 5 weeks at 25±2°C (accelerated, finished);
• up to 5 weeks at 37±2°C (accelerated, finished).

Available results show that the bulk could be stable for five weeks under 25±2°C and one week under 37±2°C. A long-term study at 2-8°C is still ongoing, 6 months results have been made available so far and found compliant to specifications. Results of ongoing stability studies will be provided post recommendation as soon as they become available.

Drug Product

Composition, manufacture and controls of excipients, intermediates and drug product
Based on antigen potency and target formulated content (6.5 U/dose), the drug substance is formulated with an aluminium hydroxide-based adjuvant and Phosphate Buffer Solution (PBS) into final bulk (FB), later filled in pharmaceutical grade 1-mL glass Pre-Filled Syringes (PFS) or 2-mL borosilicate vials which
are then inspected, labelled, and packaged. Each syringe/vial contains 0.5 mL of the final COVID-19 vaccine BIBP vaccine product, the components in the final vaccine product are: disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate, sodium chloride, aluminium hydroxide and inactivated SARS-CoV-2 antigen.

The vaccine is stored and transported at 2 to 8°C. Upon storage, precipitation can be observed and easily dispersed by shaking.

The Drug Product (DP) is manufactured in classified cleanrooms with conventional level of biosafety as follows:

1. formulation of components listed above into FB, during which the antigen is adsorbed on the adjuvant. The validated holding time of FB is not more than 72 hours;
2. filling of 0.5 ml of FB into pharmaceutical grade PFS or 0.6 ml pharmaceutical grade glass borosilicate vial;
3. visual inspection followed by packaging.

One batch of DS is used to formulate one batch of FB which is subsequently converted into 150 000 to 200 000 doses for PFS and 150 000 to 170 000 doses for vials.

In early stages of vaccine development, the target antigen content of finished product was expressed in terms of protein quantity and defined as 4 µg/0.5 ml in accordance with phase I/II clinical study results. Along with the development of the product, this target was changed to be expressed in terms of antigen quantity according to the request from NMPA and adjusted to 6.5 U⁶/0.5mL.

Control of FB is performed with validated/verified methods derived from Ph.Eur. or Chinese Pharmacopeia (CP) or developed in house. Excipients and finished product are controlled in house, based on validated/verified methods derived from CP or Ph.Eur or developed in house. The references used to control DP are developed either in house or purchased.

Discussions have been conducted with the manufacturer to clarify antigen content determination in the quality control scheme of final product. This is actually assessed indirectly by in vitro potency and expressed as unitless range, though the official antigen content claim in the product insert is a nominal value (6.5 U/dose). Conversion from potency to antigen content is obtained with a formula where the claimed antigen content of the standard is multiplied by the relative potency result of the sample. Plotting on a Shewhart chart showed that some batches had a content in antigen below claimed 6.5 U/dose. Consequently, the applicant was requested to express the specification in the product insert with a range based on results from batches used in clinical studies instead of a nominal range to match the reality of the quality control. Assurance that the lower limit of range is thought to be still clinically efficacious and immunogenic was also required. The manufacturer eventually provided satisfactory answer to these requests.

**Stability**

The following studies have been planned on both presentation of the DP:

- up to 42 months at 2-8°C (long term, still ongoing);

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⁶ U = Unit
• up to 120 days at 25±2°C (accelerated, still ongoing for vials);
• up to 28 days at 37±2°C (accelerated, finished).

Available results show that the finished product could be stable for 120 days (PFS) and 90 days (vials) at 25±2°C and for 21 days (both PFS and vials) at 37±2°C. Long term study is still ongoing, 6 months results for PFS and 3 months results for vials have been made available so far and found compliant to specifications. Results of ongoing stability studies will be provided post recommendation as soon as they become available.

The manufacturer also provided stability data for pilot scale batches which shows that the product is stable for 12 months. Additional linear regression showed that a shelf life of 24 months could be claimed. This was found acceptable.

3.2 Inspection overview

An international inspection team of experts from WHO, South Africa and observers from the NMPA and BJMPA of China performed a GMP inspection, the details of which are outlined below:

Name: Beijing Institute of Biological Products (BIBP) Co., Ltd.
Address: No. 6 (East Part) and No. 9 (West Part), Boxing 2nd Road, Beijing Economic and Technological Development Area, Beijing, 100176, the People’s Republic of China
Date: 8 to 12 February 2021
Vaccines: The presentation is 1ml pre-filled syringes with 0.5 ml/syringe. A 2ml vial presentation containing 0.5 ml of vaccine is also available. Both presentations are mono dose.
Production Line: The inspection focused on the production and control of COVID-19 vaccine BIBP in the following buildings:
  o Cell culture area
  o P3 production and testing areas
  o Filling and packaging for pre-filled syringes presentation
  o Filling lines and packaging for vials presentation
  o Testing area
  o Warehousing Area for final product, raw material, excipients and packaging materials

The inspection focused on the quality management system of the site and the manufacturing and control of the COVID-19 vaccine BIBP as per WHO Good Practices guidelines and publications.

The inspection covered the following systems and areas:

1. Pharmaceutical quality system
   • Management review
   • Quality risk management
   • Product quality review
   • Deviation management
   • Change control
Recommendation for an EUL of COVID-19 vaccine BIBP submitted by the BIBP Co., Ltd.

- CAPA management
- Complaints
- Product recalls
- Pharmacovigilance
- Self-inspection
- Quality audits and suppliers’ audits and approval
- Contract production, analysis and other activities
- Quality agreement
- Personnel
  - Training
  - Qualification of aseptic operators
  - Personal hygiene
- Documentation
- Batch Release Process
- Lot Summary Product review

2. Production system
   - The manufacturing process of COVID-19 vaccine BIBP
   - Seed lots
   - Cell banks
   - Intermediates and drug substances
   - Formulation
   - Filling
   - Visual inspection
   - Labelling
   - Packaging
   - Storage
   - Sterile filtration
   - Validation of the aseptic processing through media simulations
   - Process validation

3. Premises and Equipment system
   - The manufacturing and testing areas associated with COVID-19 Vaccine BIBP
     - Cell culture area
     - P3 production and testing areas
     - Filling and packaging for Pre-filled Syringes presentation
     - Filling lines B, C, and D, and packaging for vials presentation.
     - Testing area.
     - Warehousing Area for final product, raw material and excipient and packaging material.
   - Waste management
   - Qualification and validation
   - Water system production
   - Pure Steam
   - Heating, Ventilation, and Air Conditioning (HVAC) System
   - Steam sterilization by the autoclaves
   - Vial washing machine
Recommendation for an EUL of COVID-19 vaccine BIBP submitted by the BIBP Co., Ltd.

- Depyrogenation Tunnel
- Filling and stoppering machine
- Capping machine
- Visual inspection equipment
- Cleaning

4. Laboratory control system
5. Materials system
6. Packaging and labelling system
7. International shipping arrangement

Upon completion of the inspection a WHO Inspection Report was issued to the manufacturer detailing the findings and listing all deficiencies identified in order of severity. Manufacturers are provided with a timeline to respond to the report. During the final review, WHO considered the Corrective and Preventive Actions (CAPA) proposed and undertaken by the manufacturer.

3.3 Nonclinical overview

Twelve nonclinical studies have been conducted to assess the efficacy, immunogenicity and safety of BIBP COVID-19 Vaccine. These were conducted in non-human primates (protective efficacy and safety), mice, rats and guinea pigs (for immunogenicity studies, including adjuvant, and safety studies). A reproductive toxicity study in rats did not detect any unexpected abnormalities in dams or the offspring.

Efficacy
The protective effect assessment of the vaccine in 8 rhesus macaques (4 of whom received low dose and 4 high dose, 0/14-day schedule) plus 2 unvaccinated controls was performed by the Institute of Medical Experimental Animals of Chinese Academy of Medical Sciences (contract research organization of BIBP). High levels of neutralizing antibodies were associated with protection against SARS-CoV-2 challenge – no viral replication in the lungs was shown –, and antibody-dependent enhancement (ADE) was not observed.

Immunogenicity
BIBP conducted mouse/guinea pig immunogenicity study for COVID-19 Vaccine BIBP inactivated bulk, mouse immunogenicity study with aluminum hydroxide [Al(OH)₃] for COVID-19 Vaccine BIBP bulk, mouse/rat immunogenicity study for COVID-19 Vaccine BIBP final product, and different animal models immunogenicity study for COVID-19 Vaccine BIBP final product. These small animal immunogenicity studies demonstrated immunogenicity, value of adjuvant in improving immune responses, superiority of 2-dose immunization regimens, and batch-to-batch consistency of immunizing potency.

Safety
Single-dose toxicity study for Sprague Dawley (SD) rats with intramuscular injection, repeat-dose toxicity study for SD rats with intramuscular (IM) injection, repeat-dose toxicity study for Macaca fascicularis with IM injection, repeat-dose reproductive toxicity study for SD rat with IM, systemic active anaphylaxis study for guinea pig were conducted by JOINN Laboratories (Beijing), Inc. Neither abnormal clinical observations nor animal death/impending death were observed in negative control groups and test article groups. The maximum tolerated dose (MTD) was determined to be equal or greater than 24 µg/rat, which is about 900 times of the clinically planned dose. In the repro-tox study, in rats, no abnormalities
in vaccinated males, vaccinated females or offspring were detected. No evidence of systemic sensitization for anaphylaxis was detected in the guinea-pig sensitization study.

## 3.4 Clinical overview

The evidence to support the COVID-19 Vaccine BIBP comes from interim results of a phase 1/2 study (COVIV01), conducted in individuals from 3 years of age, which included 2128 participants in China and 112 in Pakistan; a phase 3 study (COVIV02), conducted in the United Arab Emirates (UAE), Bahrain, Egypt, and Jordan, involving 45000 participants 18 years of age and above; and a double-blind randomized study (COVIV05) conducted in China aimed at immunological bridging of commercial scale and pilot scale vaccines and the assessment of lot-to-lot consistency.

COVIV01 and COVIV02 were designed as double-blind, randomized, placebo-controlled-trials and are still ongoing. In COVIV01, three formulations (low dosage – 2 µg/0.5 mL/dose –, middle dosage – 4 µg/0.5 mL/dose –, and high dosage – 8 µg/0.5 mL/dose –, and different combinations of number of doses and intervals between doses (1-dose schedule, 2-dose schedule – 14, 21, or 28 days apart –, and 3-dose schedule 21/28 days apart) were studied. In this study, a total of 96 subjects ≥ 60 years participated in phase I and 240 in phase 2 with 3-dose schedule 28 days apart. In COVIV02 15000 participants received two doses of COVID-19 Vaccine BIBP 4 µg/0.5 mL on days 0 and 21, and 15000 received placebo (containing aluminium hydroxide). The remaining 15000 received another experimental COVID-19 vaccine, manufactured by the Wuhan Institute of Biological Products, and will not be further discussed here.

Two other phase 3 studies are also ongoing, but no results are said to be available. These are double-blind, randomized, placebo-controlled-trials conducted in Peru (COVIV03) and Argentina (COVIV04) in, respectively, 6000 and 3000 participants from 18 years of age.

### 3.4.1. Vaccine efficacy

COVIV02 was conducted to evaluate the immunogenicity, safety and protective efficacy of two doses (21-day interval) of COVID-19 Vaccine BIBP in healthy people aged 18 years and above.

Only data from interim analyses of the COVIV02 trial were submitted to WHO. The first interim analysis was conducted after >50 cases occurring after the second vaccine dose were identified, based on the data as of 31 October 2020 and the protective efficacy data as of 30 October 2020. The median follow-up of the participants at the time of this first interim analysis was only 35 days, which was considered insufficient.

A second interim analysis of the COVIV02 study, when data was available for 13765 participants in the vaccine group (11642 males, 13556 aged 18-59 years) and 13765 participants in the placebo arm (11642 males, 13559 aged 18-59 years) with a median follow-up at the time of data lock of 112 days was carried out when there were 116 cases, 21 out of them in the COVID-19 Vaccine BIBP arm and 95 in the control arm. For the primary analysis (laboratory-confirmed symptomatic COVID-19 cases 14 days after the second dose of the vaccine) the estimated protective efficacy was 78.89 % (95% CI 65.79%, 86.97%). Vaccine efficacy, calculated taking into consideration the person-years of follow-up, was 78.07% (95% CI 64.82%, 86.33%). Vaccine efficacy estimates were similar in males and females (point estimates of 78.4% and 75.6%, respectively). Vaccine efficacy in the elderly could not be estimated given that there were no
cases in the vaccine and placebo arms. Available data were also not sufficient to estimate vaccine efficacy for participants with comorbidities and for severe COVID-19 cases (only 2 severe cases were observed in the placebo arm and none in the vaccine arm).

3.4.2. Vaccine safety

In the COVIV01 study there were no significant differences in the incidence of total adverse events (AEs) and systemic adverse reactions among the study arms. Systemic AEs were mainly fever, and local AEs were mainly pain. No ≥grade 3 AE was reported in the vaccine arms. Serious adverse events (SAEs) were reported in 12 participants; all were assessed as unrelated to the vaccine.

In the second interim analysis of the COVIV02 study, as of 31 December 2020 43851 and 42501 participants had completed, respectively, the first and second vaccine or placebo doses. Among the 14634 participants who received the vaccine 6570 experienced a total of 16057 AEs, for an incidence of 44.90%, which was comparable to the placebo arm (49.01%). Solicited AEs were reported in 20.45% and 22.25% of the vaccine and the placebo groups, respectively. There were 73 ≥grade 3 AEs in the vaccine group (0.39%), and 73 (0.43%) in the placebo arm. The incidences of SAEs in the vaccine and placebo groups were also comparable (0.40% vs. 0.55%). Two SAEs were considered to be possibly causally related to the vaccine (serious nausea and inflammatory demyelination syndrome / acute encephalomyelitis. In adults 60 years of age and older the safety profile was comparable to that of younger adults, but they presented lower reactogenicity. In this age group no SAE was observed.

In the bridging study (COVIV05) no significant differences were observed between the AEs reported from participants receiving vaccines produced at commercial scale and pilot scale.

By WHO request BIBP provided safety information about post emergency use authorization (EUA) use of their COVID-19 vaccine in China. According to BIBP, as of 8 March 2021, 35.37 million people had received at least one dose of COVID-19 Vaccine BIBP in China, by then there were 6918 reports of adverse reactions, including 4633 general adverse reactions. The overall incidence of adverse reactions was 19.56/100 000 doses, and the incidence of general reactions was 13.09/100000 doses. No post-EUA surveillance data was available from the UAE.

3.4.3. Immunogenicity

In the COVIV01 study the mid-dose (4µg/0.5mL) provided 100% seroconversion of neutralizing antibodies in participants 18-59 years of age and 100% in the participants ≥60 years at 28 days after the second dose. Cellular Immunity: The vaccine did not cause “obvious” inflammatory factor storms or abnormal proliferation of cellular responses. Antigen-specific cellular immunity was not reported. According to BIBP, current results show that antibody levels did not decrease 3 months after vaccination (GMT being 233.6 [95% CI 176.2, 309.7] 28 days after the second dose, and 273.9 [95% CI 202.8, 370.0] 90 days after vaccination).

In the second interim analysis of the COVIV02 study seroconversion of neutralizing antibodies in the vaccine group was 100% (95% CI 99.56, 100) compared to 16.07% (95% CI 13.64, 18.74) in the placebo group. Neutralizing antibody GMT were 152.6 (95% CI 146.0, 159.4) in the vaccine arm and 2.1 (95% CI 2.1, 2.2) in the placebo arm. Total binding antibody GMTs were 1366.1 (95% CI 1249.7, 1493.3) and 8.9 (95% CI 8.1,9.8), respectively, in the vaccine and in the placebo arms. When stratified by age,
seroconversion rates (neutralizing antibodies) were 99.52% and 100%, respectively, in the 18-59 and ≥60 years of age groups. GMT titers were lower in those over 60 years (109.7, 95% CI 97.4, 123.4; N=42) as compared to 18-59 years (156.2, 95% CI 149.8,163.0; N=838).

Cross-neutralization studies with 10 SARS-CoV-2 isolates from China and other countries (but not qualified as Variants of concern) indicate that the sera from the participants could neutralise all these viral isolates. In an independent study\(^7\), neutralizing antibody titers against pseudo-typed viruses expressing the spike protein of SARS-CoV-2 wild-type and variants were reported. Titers against the wild-type pseudotyped virus in sera from BIBP vaccinees and in convalescent patients were comparable, though both were of low magnitude. Twenty out of 25 BIBP vaccinee serum samples showed complete or partial loss of neutralization against the B.1.351 pseudovirus, however neutralization was maintained for the B1.1.7 and D614G pseudoviruses.

### 3.4.4. Special populations

Regarding special populations, as mentioned above, efficacy in individuals over 60 years of age could not be assessed due to small numbers.

Some subjects with comorbidities were enrolled, and data are available for participants with hypertension, diabetes and BMI ≥30. Vaccine efficacy was demonstrated amongst participants with BMI ≥30 of 80.7% (95% CI 56.7%, 91.4%). For hypertension and diabetes, there were more cases in the placebo group than the COVID-19 vaccine BIBP group, however the number of cases were too low in these populations to reliably assess efficacy.

Pregnant/lactating women were excluded from the studies, therefore efficacy, immunogenicity and safety of COVID-19 Vaccine BIBP in these groups is currently unknown. No studies have been conducted on co-administration with other vaccines and on interchangeability or sequential use with other COVID-19 vaccines.

### 3.5 Risk Management Plan

### 3.5.1. Product description

Acceptable

### 3.5.2. Nonclinical information

Acceptable

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3.5.3. Clinical information

a. Important identified risks:

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<tr>
<th>BIBP</th>
<th>WHO</th>
<th>Comments</th>
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<td>- Pain at the vaccination site</td>
<td>Anaphylaxis</td>
<td>Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15 minutes of observation is recommended for each vaccine after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions</td>
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<td>- Swelling at the vaccination site</td>
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b. Important potential risks:

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<tr>
<th>BIBP</th>
<th>WHO</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Dependent Enhancement Effect (ADE) or Vaccine Related Enhancement Disease (VED)</td>
<td>Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)</td>
<td>There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for BIBP’s inactivated COVID-19 vaccine, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.</td>
</tr>
<tr>
<td></td>
<td>Programmatic errors</td>
<td>Minimizing this situation in advance under real use conditions may be necessary. This should be monitored via routine pharmacovigilance activities and be presented in each Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Updated Report (PSUR)</td>
</tr>
<tr>
<td>- Pain at the vaccination site</td>
<td>Reactogenicity</td>
<td>There is a list of several AEs classified by applicant as identified risks because of the frequency, but the proportion of AEs were higher in the placebo group than</td>
</tr>
</tbody>
</table>
− Swelling at the vaccination site
− Redness at the vaccination site
− Induration at the vaccination site
− Rash at the vaccination site
− Itch at the vaccination site
− Headache
− Fever
− Muscle pain
− Arthralgia
− Cough
− Dyspnoea
− Nausea
− Diarrhoea
− Skin pruritus
− Fatigue
− Allergic reaction

the vaccine group, probably it was because a nocebo (7) effect. This does not necessarily mean that the vaccine is safer than placebo, but probably it is because of the limited experience with the vaccine from clinical trials. Additionally, overview of safety information is limited to written descriptions of adverse events, without information on numbers of exposed or the description of relevant cases. The identified risks need to consider frequency but also the importance in seriousness, severity and impact.

c. Missing information:

<table>
<thead>
<tr>
<th>BIBP</th>
<th>WHO</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women and lactating women</td>
<td>Use during pregnancy and while breastfeeding</td>
<td>Pregnant and lactating women not included in the clinical trials</td>
</tr>
<tr>
<td>Subjects being infected and with previously infected experience</td>
<td>Current or past SARS-CoV-2 infection</td>
<td>To be assessed in a post-emergency use or post-marketing study</td>
</tr>
<tr>
<td>Use in immunocompromised patients</td>
<td>Use in immunocompromised patients, including people living with HIV.</td>
<td>This population was excluded from the clinical trials.</td>
</tr>
<tr>
<td>Subjects aged 60 and above</td>
<td>Subjects aged 60 years and above</td>
<td>Current ongoing clinical trials include only a small proportion of participants aged 60 years and above, from whom sufficient safety and efficacy data have not yet been obtained. When this vaccine is deployed on a large scale after emergency use approval and/or marketing authorization, it is likely that the elderly will be vaccinated. In fact, it is likely that they are considered a priority group for vaccination. Current data support vaccine use limited to the age group of 18-59 years</td>
</tr>
<tr>
<td>Subjects with chronic diseases such as</td>
<td>Use in patients with comorbidities (e.g.,</td>
<td>Patients with comorbidities have not been included in the clinical trials and</td>
</tr>
<tr>
<td>Condition/Consideration</td>
<td>Relevant Information</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Diabetes, renal dysfunction or hepatic dysfunction</td>
<td>Relevant information about the use of the vaccine in them is missing.</td>
<td></td>
</tr>
<tr>
<td>Safety of subjects with acute disease, acute attack of chronic disease, severe chronic disease, allergic constitution and fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-administration of BIBP’s COVID-19 vaccine with other vaccines</td>
<td>Interaction with other vaccines The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g. influenza) has not been evaluated.</td>
<td></td>
</tr>
<tr>
<td>Subjects aged 18 and younger</td>
<td>Use in pediatric population &lt;18 years of age No efficacy data are available from participants aged &lt;18 years of age.</td>
<td></td>
</tr>
<tr>
<td>Immune function deficiency subjects</td>
<td>Use in patients with autoimmune or inflammatory disorders There is limited information on the safety of BIBP’s inactivated COVID-19 vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease. Autoimmune and inflammatory disorders are important missing information and as these terms are not synonyms, they should be addressed separately.</td>
<td></td>
</tr>
<tr>
<td>Subjects aged 18-59 long-term safety data</td>
<td>Long-term safety profile of BIBP’s inactivated COVID-19 vaccine is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information.</td>
<td></td>
</tr>
<tr>
<td>Impact of the emergence of variants on vaccine efficacy/effectiveness and safety</td>
<td>BIBP should provide to WHO any data on immune response or efficacy against infection with new emerging variants, particularly data from vaccine breakthrough cases as soon as available, irrespective of source.</td>
<td></td>
</tr>
</tbody>
</table>
3.5.4 Pharmacovigilance Plan

Routine pharmacovigilance activities: Acceptable in general, adverse reaction reporting, and signal detection are in accordance with national and international Good Pharmacovigilance (GPV) guidelines.

The monitoring of adverse events (AEs) of interest should consider facial paralysis, Guillain-Barre Syndrome and neurological disorders, coagulation disorders (thromboembolism, haemorrhage), reactogenicity following vaccination and all serious adverse events, as included in routine pharmacovigilance in the submitted RMP.

There is a general concern about the collection of AEs in low- and middle-income countries (LMICs) of certain regions, because of the need for adequate pharmacovigilance systems and the limited information in the clinical trials.

Therefore, routine pharmacovigilance activities should be implemented in all WHO regions considering the limitation of reporting and the access to the tools to ensure the implementation of reporting. The spontaneous reporting needs to be preferably harmonized in most of the countries through the VigiBase platform.

Signal detection is proposed, BIBP plans to prepare a Summary Monthly Safety Report to submit to WHO in complement to the submission of Periodic Safety Update Reports (PSURs). Additionally, this monthly safety report should contain the following:

1. Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g. pregnant women, immunocompromised);
2. Total number of adverse event reports by country, WHO regions and globally;
3. Exposure data stratified by country including any available data on age groups, comorbidities, race, ethnicity, etc.;
4. Changes to reference safety information in the interval;
5. Ongoing and closed signals in the interval;
6. List of adverse events of special interest and safety concerns identified in the RMP (including the additional missing information) – numbers and relevant cases, including time-to-onset and observed/expected analyses;
7. Fatal reports – numbers and relevant cases, including observed/expected analyses;
8. Vaccination failure / lack of efficacy (including confirmed and suspected cases) reports and vaccination errors (categories according to preferred terms);
9. Potential interaction with other vaccines/concomitant treatments-number and relevant cases;
10. Summary outcomes of some of the routine pharmacovigilance activities (applied in the WHO context) for the purpose of rapid signal detection and communication activities. Summary of all ongoing registries and studies in the six-month scheduled PSURs, unless a safety signal is identified that requires immediate regulatory action; and

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For traceability, the applicant should create “Traceability and Vaccination Reminder cards”, printed cards to vaccinators, that may be completed at the time of vaccination when necessary. The applicant is requested to implement appropriate methods to ensure adequate traceability. The applicant should provide a detailed description of shipping conditions including automated temperature and location logging. The applicant should include labelling and examples of the 2D barcode and vaccination certificate.

In addition, the applicant is requested to monitor and evaluate the impact of emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of BIBP’s inactivated COVID-19 vaccine and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

As part of the additional pharmacovigilance activities, BIBP is committed to conduct six clinical studies on the protective effectiveness of the vaccine – among the elderly, among subjects with comorbidities, among special populations, and among pregnant women and lactating women. According to BIBP these trials will be implemented with established timelines. The real-world studies will be conducted in collaboration with IVI, Fudan University and Chinese CDC; clinical studies will be implemented in close collaboration with the relevant health authorities of the countries where the vaccine is being used, and the protocols and study reports will be submitted to WHO. These clinical studies are as follow:

1. Real-world vaccine effectiveness: Real world study in subjects 18 years old and above in different countries of UAE, Mongolia, Serbia, Hungary, and Morocco to evaluate effectiveness and safety of COVID-19 Vaccine BIBP in subjects aged 60 years old and above. Studies will concentrate on effectiveness and safety among people over 60 years old in different geographic regions, including LMIC. A report will be available in December 2021.

2. International Vaccine Institute (IVI) Protective Effectiveness Studies: a set of studies will be led by IVI in collaboration with BIBP. These studies will compare vaccine effectiveness with another COVID-19 vaccines that has been listed by WHO-EUL. IVI-led will assess protective effectiveness and safety of Covid-19 vaccine BIBP against variants, immunogenicity of a vaccination series using different COVID-19 vaccines, and safety and immunogenicity among special population, including people with HIV. A report will be available on December 2022.

3. Large-scale active safety surveillance: The safety of the Covid-19 Vaccine BIBP will be evaluated through active monitoring of 105,000 vaccinated individuals, focusing on people with chronic medical conditions, people aged 60 years and above, and pregnant and breastfeeding women. A report will be available in June 2022.


5. Co-administration: Evaluate the safety, immunogenicity, and possible immune interference of Covid-19 Vaccine BIBP co-administered with influenza vaccine and 23-valent polysaccharide pneumonia vaccine. A report will be available in January 2022.

6. Large-scale Passive Safety Surveillance: Safety information is being collected from 1 million subjects through China’s AEFI passive surveillance system to evaluate safety of the vaccine, paying particular attention to rare adverse effects, including AESI, SUSAR and SAE, with a particular focus on assessing presence of ADE/VED. A report will be available in December 2021.
3.5.5 Risk minimization activities

The routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product. Large scale mass vaccination may potentially introduce the risk of medication errors related to storage, handling, dosing, and administration errors associated with a multi-dose vial, and confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC (product insert). The applicant could consider, to minimizing the risk of immunization errors, educational support (for example printed posters / guides / instructional material), establish adequate communication with vaccine responsible programs in the country or any other initiative that could be helpful to avoid or minimize this potential risk.

4 Outcome of review

4.1 Quality

The critical quality issues were satisfactorily resolved. The few remaining issues are considered to have minor impact on the quality of the product (see section 10.1) and therefore can be addressed post listing.

4.2 Inspections

The site inspection was carried out at BIBP and several deficiencies of varying severity were identified, documented that categorized according to criticality and impact on GMP compliance.

The inspection at BIBP revealed no critical deficiency, 5 major deficiencies grouping 41 issues, along with 7 other deficiencies grouping 19 issues. These non-compliances included but were not limited to the major deficiencies presented below.

Major deficiencies identified during the inspection.

1. There were unmitigated risks to the quality of the product resulting from poor design of the process, insufficient process validation studies and poor control strategy throughout the manufacturing process.
2. There were unmitigated risks of contamination to the product throughout the manufacturing process and insufficient controls in place.
3. The design of the facility, equipment and procedure in place were found deficient.
4. The gowning of the aseptic operators and the aseptic behaviour in aseptic rooms during the aseptic filling of the vaccines were found deficient.
5. The qualification and validation of the facility, equipment and manufacturing process were found inadequate.
6. The quality management system was found deficient for the elements below:
   - The Quality Risk Management (QRM)
   - The investigation of complaints
   - The management of the Out of Specifications and Out of Trend test results
   - The management of the incidents
   - Poor documentation and records management practices
The manufacturer BIBP was provided with a detailed inspection report listing the non-compliances with a request to propose and undertake Corrective and Preventative Action (CAPA) to address these deficiencies.

Subsequently, BIBP has undertaken substantial remedial actions to address the issues listed in the inspection report. The actions taken and proposed to be taken along with the commitments to correct the deficiencies have been reviewed by the PQT Inspection Team. Following the review, the Prequalification Inspection Team will recommend that the site can be considered to be compliant with the standards of GMP published by the WHO.

BIBP site was officially informed by WHO on 8 April 2021 on its GMP compliance status and acceptance for the following activities:

- Manufacture of drug substances and finished bulk vaccines.
- Aseptic filling and packaging into small volume containers of axenic vaccine.
- Analytical, biological, microbiological and animal testing of drug substance and other raw materials associated with intermediates and finished vaccines.

Of importance to note is that since several major deficiencies were made during the inspection, WHO wishes to remind the company that the improvements outlined in the corrective measures must be robustly implemented and the improved level of GMP compliance, sustained. In addition to regular monitoring and follow up, WHO will verify the effective implementation of the improvements by performing the next inspection of BIBP operations within 12 months.

4.3 Clinical

This clinical assessment raised a series of queries and comments from the reviewers on different aspects of the nonclinical and clinical submitted evidence, as well as on issues related to the RMP. Two rounds of nonclinical and clinical questions were submitted to BIBP, and most of the clarifications and additional information required were provided.

From the clinical point of view the TAG EUL recommends that an EUL may be granted by WHO to COVID-19 Vaccine BIBP for “active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 18 to 59 years of age”. The current clinical trial efficacy estimates and reduced immunogenicity findings in individuals 60 years of age and older do not support the indication of COVID-19 Vaccine BIBP in age groups other than adults 18-59 years of age. Additional evidence should be obtained from interventional or observational studies to assess whether COVID-19 Vaccine BIBP could also be indicated for use in individuals 60 years of age and above, in individuals with different comorbidities and immunocompromised individuals (including people living with HIV), and in pregnant/lactating women. The need and timing for a boosting dose can be assessed in a subset of participants on the ongoing clinical trials and post-listing studies.

Changes in the RMP and product insert, as pointed out in this report, need to be made.

The following commitments were agreed upon by BIBP as a necessary condition for the granting of an EUL for BIBP COVID-19 vaccine.
1. The applicant should submit to WHO the final clinical study reports of the ongoing studies (COVIV01 and COVIV02, the latter planned to start to be prepared in June 2021) whose interim analyses have been presented as part of this application, as well as COVIV03, conducted in Peru, and COVIV04, conducted in Argentina, once they become available.

2. The applicant should submit to WHO the full reports of the test-negative design case-control study conducted in Bahrain by the local Ministry of Health, which estimated vaccine effectiveness including population 60 years of age and older, and of the two effectiveness studies conducted in the UAE as soon as they become available.

3. The applicant is urged to encourage trial participants who are not deemed to be at substantial risk of SARS-CoV-2 infection and COVID-19 morbidity or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine, to remain enrolled in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine, with full acknowledgment that the trial participant has a right to withdraw from the trial at any point, without penalty. The applicant should send WHO monthly safety reports, and Periodic Safety Update Reports (PSURs) every 6 months in the first year post-EUL, followed by annual reports thereafter.

4. The applicant should send WHO the report the outcome of the cases of pregnancy observed in the clinical studies as part of the PSURs.

5. The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy/effectiveness of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351, P.1, B.1.617, and others). This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.

6. The applicant should make the changes in the product insert as addressed in section “5 Technical considerations” of this report, including but not limited to: the vaccine indication limited to adults from 18 to 59 years of age; exclusion of pregnant and lactating women as vaccine contraindications; change of the “observation time after vaccination” for “at least 15 minutes” instead of “at least 30 minutes”; change of the text about vaccine use in pregnancy and breastfeeding. The product insert should be revised for technical terminology adequacy.

7. The applicant should conduct, within the estimated timelines, the following studies: a) CNBG-RWS-001 (to be conducted in the UAE, Mongolia, Serbia, Hungary and Morocco to evaluate effectiveness and safety of COVID-19 Vaccine BIBP in subjects aged 60 years old and above); b) IVI-006 (set of studies led by the International Vaccine Institute – IVI – in collaboration with BIBP on expanding access and delivery of COVID-19 Vaccine BIBP in Mozambique); c) CNBG-RWS-002 (post-authorization active surveillance study to evaluate the safety and immunogenicity of COVID-19 Vaccine BIBP); d) CNBG-RWS-003 (post-authorization active surveillance phase IV study to evaluate the safety of COVID-19 Vaccine BIBP in special populations); e) CNBG-CIP-004 (randomized, controlled, multicenter trial of simultaneous administration of COVID-19 Vaccine BIBP, 23-valent pneumococcal polysaccharide vaccine, and tetravalent influenza vaccine); f) CNBG-RWS-005 (post-authorization passive surveillance phase IV study to evaluate safety of COVID-19 Vaccine BIBP); g) cross-neutralization studies to investigate breakthrough COVID-19 cases in China and overseas. The issue of the need and timing for a boosting dose of the vaccine should be addressed. These studies are considered additional pharmacovigilance activities. Periodic follow-up reports on these studies should be sent to WHO as part of the PSURs or earlier, whenever appropriate.
8. Regarding the Risk Management Plan, under “safety specifications”: a) the text of “identified risks” should be aligned with the table in section 3.4.3, and “anaphylaxis” should be added; b) the text of “potential risks” should be aligned with the table in section 3.4.3, and “programmatic error” and “reactogenicity” should be added; c) the text of “missing information” should be aligned with the table in section 3.4.3, and “use in immunocompromised patients including patients living with HIV”, “use in patients with comorbidities”, “impact of the emergence of variants of concern on vaccine efficacy/effectiveness and safety” should be added; d) “interaction with other vaccines” and “interchangeability” should be considered separately from each other.

9. Regarding the Risk Management Plan, under “Pharmacovigilance Plan”: a) as part of the routine activities, “Traceability and Vaccination Reminder cards” should consider differences between regions or countries and the applicant should submit the tools and process to implement this; b) the manufacturer should clarify how adverse events / safety information will be collected as this may vary depending on different health and pharmacovigilance systems; the clarification must address how the quality of the information will be warranted wherever the vaccine is used; c) the protocols of the studies considered as additional pharmacovigilance activities should be included in the Pharmacovigilance Plan and shared with WHO.

10. Regarding the Risk Management Plan, under “Risk minimization activities”, the company should present regional annexes that ensure the correct implementation of risk minimization activities given the differences between regions or countries. These should include: a) guidance on the requirements of the dosing station or facilities, the equipment needed and the training of the dosing staff, specially to attend cases of anaphylactic shock; b) a minimum period of 15-minute of observation after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.

11. In addition to the above, the company is required to: a) report serious adverse events following immunization (within 15 days of receipt of the report); b) report quality complaints from the field for batches supplied; c) report any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA of reference (NMPA); d) report any problems/constraints in production or quality control which might affect the emergency use condition granted to this product.

5 Technical considerations

The technical considerations included in this section are those proposed by the applicant. The TAG and the PEG’s considerations are made in the “Comments” after each subsection.

5.1 Vaccine characteristics

The COVID-19 Vaccine (Vero Cell), inactivated is made from the SARS-CoV-2, 19nCoV-CDC-Tan-HB02 strain which is inoculated on the Vero cells for culturing, harvesting, β-propiolactone-inactivation, concentration and purification, then followed by adsorption with aluminium hydroxide adjuvant to form the liquid vaccine. The vaccine is free of antibiotics and preservatives. Active Composition: SARS-CoV-2, 19nCoV-CDC-Tan-HB02 strain (inactivated) Adjuvant: Aluminium hydroxide adjuvant Excipients: Disodium hydrogen phosphate, Sodium chloride, Sodium dihydrogen phosphate
Each pre-filled syringe/vial contains 0.5mL of product for each administration, each dose contains 6.5U of inactivated SARS-CoV-2 antigen and 0.3-0.6 mg/ml aluminium hydroxide adjuvant.

The recommended administration is through intramuscular route, the injection into a muscle will be preferably performed in the upper part of the arm.

**Comment**
- Pre-filled syringes are not in compliance with WHO’s critical programmatic suitability (see section 3.1, paragraph programmatic suitability);
- The antigen should be expressed as a range of 3.9-10.4U

### 5.2 Special precautions for storage and handling

Store and transport in a refrigerated (2°C-8°C) condition, protect from light. Do not freeze.

*Expiry: 24 months (Tentatively)*

*Packaging Configuration:* Pre-filled syringe assembly (with syringe needle), 1 syringe/ box; film-coated middle borosilicate glass vial, film-coated rubber stopper, 1 vial/box, 3 vials/box.

**Comment**
- Expiry should read shelf-life;
- Tentatively should not be on label;

### 5.3 Indication, warnings and contraindications

**Indication**

This product is used for adults over 18 years old.

The vaccine efficacy of this product for adults in 18-59-year-old cohort have been shown based on the interim report of the international Phase III clinical trial; The proportion of adults aged ≥60-year-old is relatively low (2.01%) in the clinical trials and will be increased in sequential clinical trials to obtain the data and provide direct evidence demonstrating the vaccine efficacy for adults of ≥60-year-old. Current available clinical trial data in ≥60-year-old have shown noticeable level of neutralizing antibodies induced by vaccination. At the time of administration, the health care provider should assess the risks based on the health conditions and possibility of exposure to the infection for the group of ≥60-year-old.

**Comment**

The indication should be limited to “adults from 18 to 59 years of age” (See item “6” of the section “Warnings”). The indication should be for “active immunization to prevent COVID-19 caused by SARS-CoV-2 virus in individuals from 18 to 59 years of age”.

**Contraindications**

1. Individuals who are allergic to any component (including excipients) of this product.
2. Individuals who have allergic reactions with vaccines before (Acute allergic reaction, angioneurotic edema, dyspnea, etc.).
3. Patients with uncontrolled epilepsy or other progressive nervous system diseases, and with a history of Guillain-Barre syndrome.
4. Pregnant and lactating women.
Comment

“Pregnant and lactating women” should be excluded from the contraindications. (See section on “Fertility, pregnancy and lactation”)

Warnings

[Special Warnings and Precautions for Use]

1. Long-term persistence of protection study is still ongoing, no data in this regard is available at present, the recommendations are based on interim data.
2. At present, the evidence of the protective efficacy of this product on people aged ≥ 60 has not been obtained. When the relevant institutions for disease prevention and control that need to use this product, the necessity of vaccination should be evaluated based on the health status and exposure risk of this population.
3. Before use, carefully check the vaccine container, label, appearance and expiration date. If there are cracks, spots, stains, scratches, blurred label on the container, and it exceeds the expiration date, the vaccine appears turbidity and other abnormality, it shall not be used.
4. Intravascular injection is strictly prohibited. There is no safety and efficacy data of the vaccine after subcutaneous and intradermal injection.
5. Drugs and equipment such as epinephrine should be available for emergency treatment in the event of an occasional severe allergic reaction. The vaccinee should be watched for at least 30 minutes after vaccination.
6. Use with caution in patients with acute diseases, acute onset of chronic diseases and fever; Delay the vaccination after the doctor’s evaluation if necessary.
7. Use with caution in patients who have diabetes and those with a history or family history of convulsions, epilepsy, encephalopathy or mental illness.
8. Use with caution in patients who have decrease in platelets or clotting disorders because of the risk of bleeding which may occur during intramuscular administration of the vaccine.
9. Use with caution in patients with impaired immune function (such as malignant tumor, nephrotic syndrome, AIDS patients, etc.) because the safety and efficacy data is not obtained, and such population should be vaccinated this product on an individual basis.
10. People injected with immunoglobulin should be vaccinated with this product at least 1 month apart, so as not to affect the immune efficacy.
11. The concomitant clinical trials on this vaccine in combination with other vaccines have not yet been conducted. Consult a physician for advice if other vaccines have to be immunized at the same time.
12. It is prohibited to use this product again if any adverse nervous system reaction occurred after vaccination.
13. There is no evidence of protective efficacy of this product for SARS-COV-2 infected persons or previous infected persons.
14. Like all vaccines, this product may not have 100% preventive efficacy for the vaccinee.
15. The vaccine is not studied in individuals with co-morbidities or specific risk factors for a more severe course of COVID-19 disease

Comments

Item 6. The following sentence should be deleted: “When the relevant institutions for disease prevention and control that need to use this product, the necessity of vaccination should be evaluated based on the health status and exposure risk of this population”
Item 9. Observation time after vaccination should be “at least 15 minutes” instead of “at least 30 minutes” in line with SAGE recommendations. Rephrase to: “The vaccinee should be observed for at least 15 minutes after vaccination.

5.4 Posology and method of administration

[Immunization Regimen and Dosage]
Two dose regimen at an interval of 21~28 days, each dose is 0.5mL. The recommended administration is through intramuscular route, the injection into a muscle will be preferably performed in the upper part of the arm. The booster immunization for this product has not been determined.

Comment
No comment.

5.5 Fertility, pregnancy and lactation

[Vaccination for Special Population]
1. Women of childbearing age: The data collected from women with unintended pregnancy in clinical trials who vaccinated this product was not enough and insufficient to determine the risk of adverse pregnancy outcomes (including spontaneous abortion).
2. Pregnant or lactating women: No clinical trial data on the use of this product in pregnant and lactating women is available.
3. Population ≥60 years old: The immunogenicity and safety data of this product in ≥60 years old cohort has been obtained from the domestic Phase I/II clinical trials, but the direct evidence for vaccine efficacy has not been obtained in the international Phase III clinical trials.

Comments
Suggested text:
- **Pregnancy**
  Limited experience exists with use of COVID-19 Vaccine (Vero Cell), Inactivated in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of COVID-19 Vaccine (Vero Cell), Inactivated in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
- **Breastfeeding**
  Unknown is whether COVID-19 Vaccine (Vero Cell), Inactivated is excreted in human milk.
- **Fertility**
  Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
- **Item number 3. Population ≥ 60 years old” should not be part of this section.
5.6 Interaction with other medicinal products and other forms of interaction

[Drug Interaction]
1. The concomitant clinical trials on this vaccine in combination with other vaccines have not yet been conducted, therefore no data regarding the interaction between this vaccine with other vaccines.
2. Combination use with other drugs: Combination use with immunosuppressive drugs, such as immunosuppressive agents, chemotherapy drugs, anti-metabolic drugs, alkylating agents, cytotoxic drugs, corticosteroids, etc., may reduce the body's immune response to this product.
   - 8 - If any drugs are being taken or recently taken, please inform the physician in time to avoid drug interaction.

Comment
No comment.

5.7 Safety profile

The safety of this product is evaluated through the domestic and international clinical trials. The domestic Phase I/II clinical trials are randomized, double-blinded and placebo parallel controlled to preliminarily evaluate the safety and immunogenicity of this product for adults over 18 years old. The international Phase III clinical trial is an international multi-center, randomized, double-blinded, placebo parallel controlled to evaluate the protective efficacy, safety and immunogenicity of this product. Researchers actively follow up the safety data of 0-21/28 days after each vaccination to observe the occurrence of adverse events and pay attention to the serious adverse events occurred within 12 months after full-course vaccination at the same time.

(The rest of this section is not copied in this report. Please see the complete product insert available in the TAG EUL subsection in BIBP folder - subfolder “Background documents “AttachmentC#5 Updated PI.pdf)

Comment
No comment.

6 Monitoring of performance of the vaccine in the field

6.1 Vaccine efficacy/effectiveness and safety Monitoring

BIBP is still following up on the participants of studies COVIV01 (conducted in China) and COVIV02 (conducted in the United Arab Emirates and neighbouring countries) whose final results are expected to be shared in due course with WHO. This should be informative about the duration of protection and about the level of neutralizing antibodies over time. Interim and final results of two other ongoing phase 3 clinical trials conducted in Peru (COVIV03) and Argentina (COVIV04) should also be submitted to WHO once available. The results of these ongoing studies are not expected to provide evidence to support the use of COVID-19 vaccine BIBP in age groups other than 18-59 years of age or in people with comorbidities given that a large proportion of the study population is likely to be <60 years of age and to be healthy.
BIBP relies on a passive adverse event following immunization (AEFI) surveillance system carried out by the Chinese Centre for Disease Control (CDC) to obtain post-marketing information about its vaccines. The same is already applicable to the post-Emergency Use Approval of COVID-19 vaccine BIBP in China. This AEFI surveillance, although covering a huge number of individuals, is limited to China. BIBP has proposed and committed to conduct a series of post-listing studies in different settings in LMICs, that are expected to provide evidence of effectiveness and safety for individuals 60 years of age and older, individuals with comorbidities, immunocompromised individuals (including people living with HIV) and pregnant and lactating women. The issues of monitoring and evaluating vaccine effectiveness against emerging variants of concern of the SARS-CoV-2, co-administration with other vaccines, and of the need and timing for a boosting dose will also be addressed according to the proposed studies.

6.2 Programmatic aspects

Vaccine vial monitor
The applicant proposes to use VVM7. Based on the available data (see above) and VVM7 requirements, the claim has been accepted.

Programmatic suitability
The proposed non-auto-disabling pre-filled syringes are not compliant with WHO requirements WHO/IVB/14.10 on programmatic suitability of candidate vaccines for WHO prequalification. The presentation has some programmatic disadvantages in developing country settings:
- It does not have an auto-disable (AD) feature to prevent re-use of the device and thus, reduce the possible spread of blood borne diseases;
- It is supplied with a separate needle, so an imbalance of numbers of distributed needles and syringes could prompt re-use of needles, with risk of blood borne diseases;
- Safe disposal of the used syringes (containing glass, rubber and metal) is more difficult than disposal of the AD plastic syringes used to deliver vaccines from a vial presentation and countries may not have the required infrastructure (e.g., high temperature incineration);
- It has a larger cold chain volume per dose than a single-dose vial presentation which could challenge a country’s cold chain capacity.

The pre-filled syringe presentation meets the same quality standards as the vial presentations and can be used under pandemic situation if Health Authorities in a recipient country consider that they have the ability to satisfactorily deal with such issues.

International shipping
Procedure and validation for international shipping are provided and meet requirements of WHO guidelines for the international shipment of vaccines.

7 SAGE recommendations

The Strategic Advisory Group of Experts (SAGE) on Immunization issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to
develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

SAGE made its interim recommendations on the use of the COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm at its plenary meeting on 29 April 2021, which were subsequently endorsed by the Director-General of WHO. The recommendations are based on randomized clinical trial (RCT) data and post-introduction observational data from Bahrain reported until the meeting. The intended use of the vaccine is in persons aged 18 years and above, without upper age limit. Recognizing the very limited data in older adults from the RCT, immunogenicity and in particular post-introduction observational data were considered for the recommendation. To make this recommendation more robust and evidence based, additional data should be generated on the safety and effectiveness of the vaccine in this age group. The WHO recommended schedule is two doses with an interval of 3-4 weeks. The need for, and timing of, additional doses is being assessed in clinical trials. The vaccine showed a satisfactory safety profile and no severe hypersensitivity and anaphylaxis reactions have been recorded in clinical trials. The efficacy of the COVID-19 vaccine BIBP has not yet been evaluated in a context of widespread circulation of variants of concern. Recommendations on addressing current knowledge gaps through further post-authorization studies have been made.

8 Regulatory oversight

COVID-19 vaccine BIBP has obtained official registration certificates in 5 countries (China, UAE, Bahrain, Bolivia, Seychelles), and emergency use authorizations in 51 countries (Algeria, Angola, Argentina, Bangladesh, Belarus, Bhutan, Brunei Darussalam, Cambodia, Cameroon, China (China, Macao SAR), Comoros, Congo, Dominica, Egypt, Equatorial Guinea, Ethiopia, Gabon, Georgia, Guinea, Guyana, Hungary, Indonesia, Iraq, Jordan, Kyrgyzstan, Lao People’s Democratic Republic, Lebanon, Maldives, Mauritania, Mauritius, Mongolia, Montenegro, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, North Macedonia, Pakistan, Peru, Senegal, Serbia, Sierra Leone, Solomon Islands, Somalia, Sri Lanka, Sudan, Turkmenistan, Zimbabwe).

9 Benefit/Risk Assessment

According to WHO, the COVID-19 pandemic has caused, as of 16 April 2021, over 138 million cases of the disease and over 2.97 million deaths.⁹ COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity will be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they remain susceptible to the virus. This scenario has been complicated by the emergence of new SARS-CoV-2 variants, whose increased transmissibility has caused concern. The

⁹ https://covid19.who.int/
development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

As for any other vaccines, adverse events following immunization can be expected. This can occur immediately following injection, caused by the reactogenicity of the vaccine materials or through allergy to some components of the vaccine. In addition, long-term ill-effects may be detected months or years following vaccination. Of concern for inactivated vaccines is vaccine ADE or VAERD due to previous evidence generated with this type of vaccine. Limited data in animal models do not indicate a propensity for the COVID-19 vaccine BIBP to induce VAERD in animal models.

COVID-19 vaccine BIBP itself has shown to be associated with adverse reactions particularly local injection site redness, pain and irritation, what is common to all injected vaccines. Systemic reactions such as headache, myalgia and fever are also reported at rates common to other injected vaccines and comparable to those observed in the placebo group. As this vaccine is produced, inactivated, purified and formulated using technologies approved for other inactivated vaccines the risks to vaccinees are known. The inclusion of aluminium hydroxide as an adjuvant is to enhance immune responses to the inactivated virus. Aluminium hydroxide is commonly used in other approved vaccines with a proven track record of safety.

This vaccine may, theoretically, have an advantage over other vaccines that specifically target only the spike protein (that includes RBD). Naturally evolving SARS-CoV-2 variants of concern with mutations in the spike protein may render the spike protein vaccines less effective, while the immune responses raised by the whole inactivated virus BIBP vaccine may continue to provide protection. However, the immune response to the spike antigen may be generally lower compared to the other vaccines and may not generate strong cellular response. Preliminary data suggest that neutralising antibodies to VoC are reduced in sera of COVID-19 vaccine BIBP vaccinated individuals. Therefore, the effectiveness of COVID-19 Vaccine BIBP against emerging SARS-CoV-2 variants may be reduced and must be monitored and evaluated.

Ongoing clinical trials in China, the UAE and a few other countries have demonstrated safety and tolerability of the BIBP COVID-19 vaccine, similar to other approved adjuvanted viral vaccines. Post-Emergency Use Approval (EUA) safety data from China, obtained from safety surveillance, suggest that COVID-19 Vaccine BIBP is safe for the use in adults.

Although no correlate of protection has been agreed upon so far, immunogenicity of COVID-19 Vaccine BIBP has been demonstrated as close to 100% seroconversion rates for neutralizing and virus-binding antibodies. Protective efficacy has been demonstrated in interim analyses of one clinical trial with significant differences in the incidence of COVID-19 in vaccinated participants compared to those who received placebo. There is limited evidence that the immunogenicity of the COVID-19 vaccine BIBP may be reduced in people over the age of 60 years but the impact on efficacy is unknown.

Protective efficacy of around 78% is estimated for adults 18 to 59 years of age but no such evidence has been provided for the individuals ≥60 years of age as relatively few persons in this age group participated in the clinical studies and no case of COVID-19 was observed in this age group in the vaccinated arm of the pivotal clinical trial. There is also limited data on safety in 60+ in clinical studies.
Vaccine efficacy has also not been reliably estimated for severe COVID-19 disease, and evidence from clinical trials is not available for individuals with co-morbidities and immunocompromised individuals (including people living with HIV). Safety data are also not available for these groups and for pregnant and breastfeeding women.

The current clinical evidence supports that the benefits of administering two doses of COVID-19 vaccine BIBP in preventing symptomatic COVID-19 clearly outweigh their risks in adults 18 to 59 years of age.

This vaccine has been deployed in several countries, where it has often been used in the elderly, who are usually seen as a priority group for vaccination. So far there is limited evidence from an unpublished test-negative case-control study conducted in Bahrain that COVID-19 Vaccine BIBP is effective in the ≥60 years age group (vaccine effectiveness estimate 91%), suggesting a benefit in people 60 years of age and above, but this data with other effectiveness studies have not been submitted to WHO. Post-EUA (passive) surveillance safety data from China indicate that the vaccine is safe. Notwithstanding the lack of effectiveness and safety data it is likely that the benefit/risk is also positive for the use of COVID-19 Vaccine BIBP in pregnant and lactating women, but such evidence is currently not available and should be produced by BIBP, perhaps in partnership with other stakeholders.

10 Conclusion

Considering the public health need to limit COVID-19 morbidity and mortality and to continue immunizing the world’s population to the largest extent possible, the introduction of new vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on the available evidence assessed, the TAG considers that sufficient data is available on administering two doses of COVID-19 Vaccine BIBP to people 18 – 59 years of age during the current pandemic, subject to post-listing commitments as indicated in the below sections.

Should additional data on safety and efficacy become available that change the benefit-risk assessment, as a result of the new variants or new data for subpopulations such as the ≥60 years age group and individuals with comorbidities the EUL recommendation could be reconsidered or changed.

10.1 Quality (CMC) perspective

The following observations are still pending:

- CTD sections to be updated
- various reports/protocols
  - validation report of YT-TP-6 shipping boxes
  - study report on leachables for bulk container
  - updated long term stability protocol
- data of ongoing stability studies
  - DS: long term
  - DP: long term (PFS+vials), accelerated 25°C (vials)
- Clarifications on the correlation between semi quantitative reading and percentage of turbidity during harvesting

Given the low impact on the overall quality of the candidate vaccine, those could be reviewed post recommendation.

### 10.2 Clinical perspective

The following commitments should be agreed upon by BIBP as a necessary condition for the granting of an EUL for BIBP COVID-19 vaccine.

1. The applicant should submit to WHO the final clinical study reports of the ongoing studies (COVIV01 and COVIV02, the latter planned to start to be prepared in June 2021) whose interim analyses have been presented as part of this application, as well as COVIV03, conducted in Peru, and COVIV04, conducted in Argentina, once they become available.

2. The applicant should submit to WHO the full reports of the test-negative design case-control study conducted in Bahrain by the local Ministry of Health, which estimated vaccine effectiveness including population 60 years of age and older, and of the two effectiveness studies conducted in the UAE as soon as they become available.

3. The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine.

4. The applicant should send WHO monthly safety reports, and PSURs every 6 months in the first year post-EUL, followed by annual reports thereafter.

5. The applicant should send WHO the report the outcome of the cases of pregnancy observed in the clinical studies as part of the PSURs.

6. The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy/effectiveness of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351, P.1 and others). This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.

7. The applicant should make the changes in the product insert as addressed in section “5 Technical considerations” of this report, including but not limited to: the vaccine indication limited to adults from 18 to 59 years of age; exclusion of pregnant and lactating women as vaccine contraindications; change of the “observation time after vaccination” for “at least 15 minutes” instead of “at least 30 minutes”; change of the text about vaccine use in pregnancy and breastfeeding. The product insert should be revised for technical terminology adequacy.

8. The applicant should conduct, within the estimated timelines, the following studies: a) CNBG-RWS-001 (to be conducted in the UAE, Mongolia, Serbia, Hungary and Morocco to evaluate effectiveness and safety of COVID-19 Vaccine BIBP in subjects aged 60 years old and above); b) IVI-006 (set of studies led by the International Vaccine Institute – IVI – in collaboration with BIBP on expanding access and delivery of COVID-19 Vaccine BIBP in Mozambique); c) CNBG-RWS-002 (post-authorization active surveillance study to evaluate the safety and immunogenicity of COVID-19 Vaccine BIBP; d) CNBG-RWS-003 (post-authorization active surveillance phase IV study to evaluate the safety of COVID-19 Vaccine BIBP in special populations); e) CNBG-CIP-004 (randomized, controlled, multicenter trial of simultaneous administration of COVID-19 Vaccine
BIBP, 23-valent pneumococcal polysaccharide vaccine, and tetravalent influenza vaccine); f) CNBG-RWS-005 (post-authorization passive surveillance phase IV study to evaluate safety of COVID-19 Vaccine BIBP); g) cross-neutralization studies to investigate breakthrough COVID-19 cases in China and overseas. The issue of the need and timing for a boosting dose of the vaccine should be addressed. These studies are considered additional pharmacovigilance activities. Periodic follow-up reports on these studies should be sent to WHO as part of the PSURs or earlier, whenever appropriate.

9. Regarding the Risk Management Plan, under “safety specifications”: a) the text of “identified risks” should be aligned with the table in section 3.4.3, and “anaphylaxis” should be added; b) the text of “potential risks” should be aligned with the table in section 3.4.3, and “programmatic error” and “reactogenicity” should be added; c) the text of “missing information” should be aligned with the table in section 3.4.3, and “use in immunocompromised patients including patients living with HIV”, “use in patients with comorbidities”, “impact of the emergence of variants of concern on vaccine efficacy/effectiveness and safety” should be added; d) “interaction with other vaccines” and “interchangeability” should be considered separately from each other.

10. Regarding the Risk Management Plan, under “Pharmacovigilance Plan”: a) as part of the routine activities, “Traceability and Vaccination Reminder cards” should consider differences between regions or countries and the applicant should submit the tools and process to implement this; b) the manufacturer should clarify how adverse events / safety information will be collected as this may vary depending on different health and pharmacovigilance systems; the clarification must address how the quality of the information will be warranted wherever the vaccine is used; c) the protocols of the studies considered as additional pharmacovigilance activities should be included in the Pharmacovigilance Plan and shared with WHO.

11. Regarding the Risk Management Plan, under “Risk minimization activities”, the company should present regional annexes that ensure the correct implementation of risk minimization activities given the differences between regions or countries. These should include: a) guidance on the requirements of the dosing station or facilities, the equipment needed and the training of the dosing staff, specially to attend cases of anaphylactic shock; b) a minimum period of 15-minute of observation after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions.

12. In addition to the above, the company is required to: a) report serious adverse events following immunization (within 15 days of receipt of the report); b) report quality complaints from the field for batches supplied; c) report any change that may have an impact on the quality, safety and/or efficacy of the vaccine or change the basis of the regulatory approval by the NRA of reference (EMA); d) report any problems/constraints in production or quality control which might affect the emergency use condition granted to this product.