REPORT ON THE EVALUATION OF THE EMERGENCY USE AUTHORIZATION APPLICATION FOR SPUTNIK V (GAM-COVID-Vac)VACCINE

1.0 Background Information on the Procedure

1.1 Submission of the Dossier

The local agent – Cedar Point Chemist, Accra – representing Joint Stock Company Generum of Russia submitted an application to the Food and Drugs Authority (FDA) for Emergency Use Authorization (EUA) application for SPUTNIK V (GAM-COVID-Vac) vaccine.

Location address: 601125, Vladimir Region, Petushinsky District, Volginsky Settlement, Ul. Zavodskaya, bldg 273.

Address of the Production Buildings:

- Vladimir Region. Petushinsky District, Volginsky settlement, Ul. Zavodskaya, bldg 273 (Production of Drug Substance (API))
- Vladimir Region, Petushinsky District, Volginsky settlement, Ul. Zavodskaya, bldg 263 (Production of Drug Substance (API) and production of finished product (Drug Product)

The Applicant applied for the following indication:

- Sputnik V vaccine for the prevention of coronavirus infection caused by the SARS-CoV-2 virus.

The legal basis for the application refers to:

Sections 118 (1) and 148 (1) of the Public Health Act, 2012, Act 851
Guidelines for Emergency Use Authorization of Medical Products
(FDA/GEN/GL-EUA/2021/04) Version 02

The application submitted is composed of administrative information, quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Emergency Use Authorization

The applicant requested consideration of its application for an Emergency Use Authorization in accordance with Section 168(3) – 170 of the Public Health Act, 2012, Act 851 as it is intended for the treatment of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognized by the World Health Organization (WHO) and Minister of Health.

In particular, the applicant stated that the submission was in response to the current global pandemic of Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus (CoV-2) infection. List of countries where EUA has been granted includes the following: Algeria, Argentina, Belarus, Bolivia, Palestine, Paraguay, Russia, Venezuela, Serbia, United Arab Emirates *and* Hungary

1.2 Steps Taken for the Assessment of the Product

An Evaluation Committee[1] chaired by Mr. Seth Seaneke Deputy Chief Executive (Health Products & Technologies Division) was constituted to evaluate the application.

Terms of Reference and Assessment Procedure for the Committee developed	16th January, 2021
Terms of Reference and Assessment Procedure for the Committee reviewed and cleared	18th January, 2021
Application, including supporting documents received on	20th January, 2021
Documents circulated on	21st January 2021
Maiden Committee meeting held on	22nd January 2021
Application Assessment on	25 -27th January, 2021
Peer Review Meeting to assess Draft Evaluation Report	28th January, 2021
Draft Evaluation Report presented to the Product Registration Committee	2nd February 2021
Decision of Product Registration Committee reached on	2nd February 2021

Timelines

The application was subjected to the FDA's non-pre-qualified product registration pathway toward documentation evaluation and subsequent Emergency Use Authorization. The timeline for processing E.U.A applications is within 15 working days from the date of receipt of application to the date a decision is communicated to the applicant by the Chief Executive Officer (C.E.O).

[1] Committee was comprised of the following members evaluating specific parts of the dossier submitted: Seth Seaneke – Chairperson (Deputy Chief Executive Officer (DCEO) –Health Products and Technologies); Eric Karikari-Boateng – (Head, Centre for Laboratory Services and Research); Edwin Nkansah – (Quality - Vaccines and Biological Products Department); Samuel Asante-Boateng – (Quality – Head, Drugs and Nutraceuticals Department); Yvonne Adu-Boahen – (Clinical – Head, Clinical Trials Department); George Sabblah – (Risk Management Plan – Head, Safety Monitoring Department); Patrick Danso – (Non – Clinical – Centre for Laboratory Services and Research); Nathaniel Nkrumah – (Quality - Drugs and Nutraceuticals Department); Adela Ashie – (Risk Management Plan – Safety Monitoring Department); and Mawunya Akpeke – (Administrative part - Vaccines and Biological Products Department)

2.0 Administrative

The application adequately addressed most of the administrative regulatory requirements. The Marketing Authorization Holder (MAH) was submitted in the dossier. The manufacturers of the Drug Substance (DS) and Finished Pharmaceutical Products (FPP), as well as their extent of manufacture were documented in the dossier. The product indication, immunization schedule, storage conditions and the commercial presentation of the product were also discussed in the dossier. The appointed local agent was also documented. The product label information was evaluated and found satisfactory. A list of countries where the product has been granted EUA (Algeria, Argentina, Belarus, Bolivia, Palestine, Paraguay, Russia, Venezuela, Serbia, United Arab Emirates *and* Hungary) was also provided in the dossier

Applicant duly completed and signed the FDA vaccine registration application form.
Although evidence on current Good Manufacturing Practices (cGMP) was submitted, applicant will be required to update the submitted GMP certificate to reflect the manufacture of Sputnik V vaccine in the facility.

3.0 Scientific Discussion

3.1 About the Product

The Sputnik V vaccine, also referred to as Gam-COVID-Vac is a two-dose adenoviral vector vaccine using two different adenoviruses for each dose, with doses administered 21 days apart. With Sputnik V vaccine, an adenovirus is altered so that it can deliver a piece of genetic material from the virus that causes COVID-19 into the body and get cells to express the spike protein found on the virus to induce an immune response. The two-dose regimen is represented as two components, components I and II. Component I includes a recombinant adenoviral vector that uses a serotype 26 human adenovirus carrying a SARS-CoV-2 protein S gene, and Component II includes a serotype 5 human adenoviral vector carrying a SARS-CoV-2 protein S gene.

Product particulars:

- **Country of origin**: Russia
- **Dosage form**: Frozen solution for Intramuscular injection
- **Storage condition**: Store in a dark place at a temperature not exceeding minus 18°C. Store in a thawed state for no more than 2 hours.
- **Shelf life**: 6 months.
- **Commercial presentation**: 3 mL (5-dose) contained in a 1 vial referred to as component I or component II with a package insert/patient information leaflet is placed in a pack made from folding-box carton as per Russian Standard (GOST 33781-2016) or from imported cardboard with a foam holder made from elastic polyurethane foam.
- **Vaccination schedule**: Sputnik V is administered in two stages: first 0.5 mL of Component I, and then, three weeks afterwards, 0.5 mL of component II

3.2 Type of Application and Aspects on Development

Generally, the FDA will issue an EUA based on the conditions below:

- The disease causative agent/item specified in the declaration of Public Health Emergency can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled Clinical Trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the agent specified in the declaration of emergency.
- The known and potential benefits outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life-threatening disease or condition that is the subject of the declaration; and
- That there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such serious or life-threatening disease or condition.

4.0 Quality

4.1 Drug Substance

A heterologous recombinant adenovirus platform using non-replicating adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors for the expression of the SARS-CoV-2 spike protein to induce humoral and cellular immune response in human to prevent COVID-19 disease

Manufacture, characterization and process controls

The genetic development of the adenoviral vectors has been described in the application. Information on the primers used to integrate mutations has been discussed adequately by the applicant. However, no detailed characterisation of the developed recombinant viral vectors (Ad 26 and Ad 5) were submitted in the quality dossier to adequately confirm the integrity of the biological drug substances. An overview of the general manufacturing process in a form of a process flow was presented, and found to comply with regulatory requirements. Critical controls points instituted along the entire manufacturing process were noted, although not adequately described in details in the dossier. No drug substance stability information, including the protocol and report was included in the quality dossier. Generally, the submitted information indicate that currently manufactured batches are of consistent quality, that is, appropriate and comparable to that of clinical development batches. However, additional data will be required with a view to confirming that the quality of future batches to be manufactured will also remain appropriate and comparable to that of clinical development batches over the entire life cycle of the product. Issues to be addressed in this regard includes; genotypic and phenotypic description/characterization of the 2 serotypes, report on viral propagation and purification, information on the source of the growth culture medium and trypsin-EDTA solution along with their corresponding certificates, certificates of master seed lot and working seed lot of Ad26 and Ad5 vectors, certificates of master cell bank and working cell bank (HEK293), information on the clearance and residual levels of penicillin and

streptomycin used in the manufacturing process, protein level profiling of the recombinant adenovirus type 26 and type5 carrying the gene for SARS-CoV-2 spike protein and sources and certificate of analysis of other starting materials.

Specification

Adequately controlled via test parameters, test procedures and batch analysis. Test parameters are acceptable to support the control of the drug substance.

Stability
The container closure system and the available stability data were found suitable at the time of the review.

4.2 Drug Product

Component I. Frozen solution of Recombinant serotype 26 adenoviral vector containing the SARS-CoV-2 protein S gene. It is a dense, solidified mass whitish in color, formulated with excipients and stored in a class 1 glass vial. After thawing: a homogeneous solution, colorless or with a yellowish hue, slightly opalescent.

Component II. Frozen solution of recombinant serotype 5 adenoviral vector, containing the SARS-CoV-2 protein S gene. It is a dense, solidified mass whitish in color, formulated with excipients and stored in a class 1 glass vial. After thawing: a homogeneous solution, colorless or with a yellowish hue, slightly opalescent.
Other ingredients (excipient) used the formulation of both component are polysorbate 80, magnesium chloride hexahydrate, EDTA disodium salt dihydrate, ethanol 95%, water for injection.

4.2.1 Manufacturing process of the Drug Product

Involves critical steps of filtration and filling, capping and sealing
Involves Filtration of Component I or II solution- bioburden prior to filtration is included as required and set at a limit of NMT 10cfu/100ml as required. Acceptable.
0.2µum filter was used with determination of bubble point pressure for filter integrity
Filter validation (sterile filter) was not submitted and should be provided. Also, evidence of validation of the sterilization process (rubber stoppers and aluminum crimps) was not submitted. A media fill simulation protocol and report were not submitted. In addition, no process validation studies were submitted. Specification and Batch Analysis was not sighted and same requested.

4.2.2 Stability protocol and report

Container Closure System for FPP

Primary packaging: 3.0 ml (5 doses) of each component are placed in neutral glass vials of hydrolytic class 1, format 2R; hermetically closed with rubber plugs, and crimped off with aluminium and plastic tamper-proof caps.

Secondary packaging: 1 vial with component I or component II with a package insert is placed in a pack made from folding-box carton as per Russian Standard (GOST 33781-2016) or from imported cardboard with a foam holder made from elastic polyurethane foam.
Compatibility of vaccine with primary CCS (rubber stopper) should be submitted with determination of safety profile of the observed leachable/extractable studies if applicable

4.3 Storage of Finished Pharmaceutical Product (FPP)

Store at a temperature not exceeding minus 18 °C (20±2 °C). Store in a thawed state for no more than 2 hours. Re-freezing is not allowed. Thawing was performed for 30mins. As a result, the applicant is requested to justify thawing for 2 hours when data was submitted for only 30mins. Although re-freezing is not allowed, applicant may share data on freeze thaw studies conducted. The current shelf life is 6 months

5.0 Non-clinical

Studies on confirmation of the safety of a therapeutic dose and a human injection schedule for use in clinical practice, identification of potential target organs in relation to which the toxic effect of the product is manifested, and the establishment of reversibility of the manifestations of toxicity, as well as determination of product safety parameters for their subsequent monitoring during a clinical trial were performed, reviewed and generally supported. Animal models used were that of two rodents; Balb C Mice and Syrian Golden Hamster and two Non-human Primate; Rhesus Macaque Monkey and Mamosset. Both models are relevant for the preclinical studies since they have been humanized to express hACE2 receptor and are infected by SARS-CoV-2 virus in the same way as humans.

In *vivo* study reports were submitted for immunogenicity and protection studies, biodistribution studies, toxicological studies. Single dose but repeat dose was submitted for MERS, local tolerance, immunotoxicology, allergenicity study. Reprotoxicity study was submitted for previous study in MERS.

The non-clinical studies performed with rodent and non-human primates have demonstrated that the candidate vaccine has efficacy against SARS-CoV-2 virus. The safety studies performed also provides additional information on the safety profile of the vaccine candidate in animals to support the initiation of clinical studies in human.

However, additional information pertinent to method validation of the ELISA method used to determine the neutralizing antibody titre of the serum/plasma of immunized Syrian Hamster and Rhesus Macaque Monkey in the immunogenicity studies, source of

reference standard and the corresponding characterization data, report of Adenovirus Vector Serotype 5 and 26 virus shedding study and the potential risk associated with transmission to third parties, validation report of the T-cell (CD4+ and CD8+) proliferation assay used to evaluate the cellular response of the vaccine will have to be submitted.

6.0 Clinical

Safety and immunogenicity studies were based on heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomized phase I/II studies from Russia. Heterologous COVID-19 vaccine consisted of two components. A recombinant adenovirus type 26 (rAd26) and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (rAd26-S and rAd5-S).

- Dosage form: a solution for intramuscular injection composition per dose (0.5ml) of component I (rAd26) and II (rAd5) administered 21 days apart.

- Indication for use: To help prevent the novel coronavirus infection (COVID-19) in adults ranging from 18 years and above.

- Contraindication: – Hypersensitivity to any component, several allergic reactions in person's medical history, presence of severe infectious and non-infectious disease or chronic disease become exacerbated, while pregnant or breast feeding and under 18 years.

- Administration: - Vaccinations are administered in two stages: First, component I and then 3 weeks afterwards, component II is given.

  For component II - Severe post vaccination complications (anaphylactic shock, severe generalized allergic reactions, epilepsy syndrome, Temp T 40℃, etc.)

- Mechanism of action: The vaccine mechanism is based on the ability of rAd26-based recombinant viral vector that carry the SARS-CoV-2-S protein gene to efficaciously transduce cells so the transduced cells start to produce the antigen. In view of the above, when the first dose (component I) is administered (IM), the rAd26-based vector enters the cell of the body, leading to the expression of SARS-CoV-2 spike protein, thereby triggering the development of SARS-CoV-2 immunity (primes). When the second dose (component II) is administered (IM), the rAd5 based vector enters the cells of the body leading to the expression of SARS-CoV-2 spike protein, thus effectively boosting the immune response to ensure a pronounced, long lasting immunity against SARS-CoV-2.

Pre-clinical data demonstrated the non-toxicity of the combination vaccine in different laboratory animals across a broad range dose. The safety shown in the preclinical does not differ from the safety indicators in the previous preclinical vaccine studies that showed satisfactory safety profile in clinical trials in healthy volunteers and therefore allows initiating clinical trials of Gam-COVID-Vac with healthy volunteers.

“Safety, tolerability and immunogenicity of Gam-COVID-Vac medicinal product, solution for intramuscular injection on healthy volunteers”- for liquid form. Studies were in 2 parts as reviewed.

Phase I Study was to evaluate safety, tolerability and immunogenicity of Gam-COVID-Vac medicinal product, solution for intramuscular injection, at various intervals after vaccination on healthy adult volunteers. 38 volunteers (18 during the first stage and 20 during the second stage). The efficacy analysis has evaluated all the volunteers who have completed the study as per the protocol.

The data obtained enabled confirmation of the proposed study hypothesis that injection of the developed vaccine induces the development of a strong immune response to the SAR-Cov-2 virus, involving both humoral and cellular components of the immunity.

Safety Analysis: The safety analysis has included 38 volunteers (all received a dose of the study product); 18 during the first stage and 20 during the second stage. A total of 295 AEs in the course of the study. 120 AEs in the first study stage (component I 60.1%; 39.9% of component II). 175 AEs were recorded in the second stage. No AE recorded during the first or second stage has resulted in the withdrawal of a volunteer from the study or cancelation of the study product. Most AEs have resulted in recovery with no consequences.

Overall, the AEs detected in the course of the first and second stages of the study are typical for most vaccine products. No severe AEs or SAEs have been registered.

“Open study of the safety, tolerability and immunogenicity of Gam-COVID-Vac Lyo drug, Lyophilizate for the solution for the intramuscular injection in healthy volunteers”- lyophilized powder.

Dosage form and strength – Lyophilizate for the solution for IM injection component 1 – 1 dose + component II 1 dose.
Phase I Study with the purpose to assess safety, tolerability and immunogenicity of Gam-COVID-Vac-lyo drug, Lyophilizate for solution for IM injection at various intervals after vaccination in healthy volunteers (adults). Methodology of this study was same as the frozen solution dosage form.

Phase I open prospective 2-stage non-randomized study in healthy volunteers. During the first stage of the study, safety of the single administration has been tested for component 1 and 2 and during the second stage, safety and immunogenicity after dual-dose prime boost injection or the component 1 and 2 have been evaluated. The second

stage began after safety assessment of first and was concluded that the efficacy analysis included all volunteers who completed the study in accordance with the protocol – 38 volunteers (18 in 1st stage and 20 in 2nd stage). The data obtained confirmed the hypothesis of the study that administering the vaccine induces the formation of an intense immune response to the SARS-Cov-2 virus and involves both humoral and cellular immunity.

On safety, the analysis included 28 volunteers (all volunteers who received the dose of the study drug) 8 volunteers at the first stage and 20 volunteers at the second stage of the study. SAEs were not reported as in the solution formulation study and AEs identified during both 1st and 2nd stages are typical for most vaccines.

PHASE III
A randomized, double- blind, placebo – controlled, multi- centre clinical study in parallel assignment of the efficacy, immunogenicity and safety of the Gam-COVID- Vac combined vector vaccine in prophylactic treatment of SARS-CoV-2 infection was also performed.
Comparator: placebo

The primary objective was to demonstrate the superiority of Gam –COVID-Vac combined vector vaccine against the SARS- CoV- 2 induced coronavirus infection compared with placebo, based on the percentage of the study subjects with coronavirus disease (COVID-19) developed up to 6 months after the 2nd dose of the Gam – COVID-Vac /placebo , as confirmed by polymerase chain reaction (PCR).

Percentage of the study subjects with COVID 19 disease developed up to 6 months after the second dose of the Gam – COVID-Vac / placebo, as confirmed by the PCR test after routine vaccination. The study vaccine′s preventive efficacy will be ≥ 50% compared with placebo, subject to the lower limit of the confidence interval of the point estimate for the primary efficacy variable > than 33%.

Number of study subjects – 40,000
Adequate inclusion and exclusion criteria were noted and acceptable. Inclusion criteria included negative test results for presence of IgM and IgG antibodies to SARS- CoV -2 by enzyme immunoassay; if available results from designated medical organization 7 days before inclusion. No COVID-19 in medical history, a negative COVID 19 test result by PCR during screening.

No known contact with COVID-19 infected persons within at least 14 days before enrolment, consent to the use of effective contraceptives during the study, negative pregnancy test, negative drugs and psychostimulants urine test at the screening visit. Negative alcohol test; no acute infection and or respiratory infection /disease within last 14 days and no evidence of vaccine –induced reactions or complications after receiving immunobiological products.

Duration of treatment and observation: Each subject′s participation in the study will take 180 ± 14 days after the first dose of Gam – COVID-Vac /placebo is administered. Analysis

following up to 12,296 subjects vaccinated with two components of the vaccine/placebo. The analysis covers 12,296 subjects vaccinated with two components of Gam-COVID-Vac /Placebo. The study enrolled volunteers 18-87 years. Mean age was 45.5 ± 11.9 years (Gam – COVID-Vac group) and 45.5 ± 11.8 years in (placebo group).

A total of 7497 males and 4799 females were included. Analysis of comorbidity data has shown that 2360 volunteers (25.9%) in the study group and 819 volunteers in the placebo group (27.3%) had commodities. For most of the volunteers, the risk of infection in both groups had been assessed as average. A physical examination at the screening visit identified 562 deviations, 30 of which were clinically significant. The most part of the finding referred to the cardiac and vascular system (348 of 562 findings or 61.9%). Intergroup comparison of these data did not find any statistical significant difference (P>0.05).

No statistically significant differences were found between the groups in the distributions by demographic and anthropometric data, comorbidities or COVID-19 infection risk.
Incidence of severity of adverse events in trial subjects within 6 months after receiving first dose of the study drug or placebo. A safety analysis included 12,296 volunteers (all volunteers were administered a dose of the study drug). A total of 8704 AEs in 4401 by the reported and verified during the study by the time of analysis. Of these SAEs, 3 SAEs were found in 60 and older (renal, colic, deep vein thrombosis and abscess in the area of the limb). 3 AEs were severe of 3 or higher in 60 and above years. All these AEs resolved.

The data available concludes that vaccine still under study has a good safety profile. So far no unexpected adverse events reported, two-fold prime-boost immunization with the Gam-COVID-Vac, led to the statistical lower morbidity in the Gam-COVID-Vac treatment group than placebo group, evidence of the efficacy (96%) of the study vaccine and dual prime-boost vaccination reduces severity of the disease.

Data submitted demonstrates the safety profile and the ability to induce humoral and cellular immune response from pre-trial to clinical trial (interim report).

7.0 Safety

Safety considerations for non-clinical, clinical studies were provided and reviewed accordingly. Generally safety report was considered adequate to assure the safety of the vaccine when administered. Additional requirements are however requested such as updated Risk Management Plan (RMP) to include data from phase III clinical trials with data lock point of November 2020, Criteria and methodologies for measuring and assessing the effectiveness of risk minimization measures described in the RMP, protocol to measure possible adverse outcomes of exposure of pregnant women who may be exposed to the vaccine including pregnancy registry. Update to summary of product characteristics requested.

8.0 Conclusion

The submitted documents did not entirely comply with the prescribed requirements in the EUA guidelines. Following evaluation, the product development document was found to be inadequate in following parts: Administrative, Quality and Non-clinical. The Risk Management Plan (RMP) submitted was also found to be missing critical data (i.e safety information in our population (sub-Saharan Africa) and information to adequately appreciate the proposed management of the risk associated with the use of the product.
The clinical data submitted was deemed adequate under the current public health emergency situation.
However, in spite of the inadequacies in the application, it was possible for the assessment team to make judgement on whether or not the benefit of the product outweighs the risk associated with the use of the product in the current pandemic situation. I assessment team arrived at a positive benefit – risk ratio.

9.0. Recommendation

Balancing the identified inadequacies in the product development documents submitted with the exigency of the pandemic, the assessment team recommended that an EUA is granted, and the applicant is allowed to furnish the FDA with the responses to the queries presented below within the validity period of the authorization.

Administrative

- Re-submit an updated Good Manufacturing Practice (GMP) certificate issued to GENERIUM Joint-Stock Company (GENERIUM JSC) located at 273 Zavodskaya Street, Volginsky, Petushinsky District, Vladimir Region, 601125 and 273 Vladimir Region, Petushinsky District, Volginsky settlement, Ul. Zavodskaya, bldg 263.

Quality

- Submit the process validation (PV) report for at least 3 production batches.

Safety

- Risk Management Plan (RMP):
    a. Submit the description of the pharmacovigilance system including details of the Qualified Person for Pharmacovigilance (QPPV).
    b. Submit the updated Risk Management Plan (RMP) to include data from phase III clinical trials with data lock point of November 2020.
    c. Submit the criteria and methodologies for measuring and assessing the effectiveness of risk minimization measures described in the RMP.
3. Submit the Summary of Product Characteristics (SmPCs) for Sputnik V Vaccine. The SmPC should include the items listed below, and should be in line with the FDA's labelling guidelines. An MS word version in addition to the PDF should also be submitted.
    a. Adverse event data should be presented per system organ classification and frequency of occurrence.
    b. This section "special indications" should be renamed to be in line with the FDA labelling guidelines.

c. Under current section “special indications”, the information on interaction with immunosuppressive should be included under drug-drug interactions, and separated from impact on driving.
d. Hypertension and contact dermatitis should be included in the list of adverse events.
e. Information on interchangeability of Gam-COVID-Vac with other COVID-19 vaccines.
f. Storage conditions of the thawed and unthawed vaccine should be clearly stated under storage in conditions in the SmPC.

4. Monitor the strain change after deployment and submit a report of this activity to enable the Authority make any needed regulatory decision on continued vaccine efficacy.