MINUTES OF THE 18TH CSC MEETING HELD ON 26TH DECEMBER 2020.

1. The 18th CSC Meeting was held on 26th December 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC) at the Committee Room, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

2. The meeting was attended by the following members: -

Sr. No.	Name	Designation
01	Dr. Abdur Rashid.	Chairman CSC / Director, Division of Pharmacy Services.

3. Following members attended the meeting online through Zoom:

01	Prof. Dr. Javed Akram.	Professor of Medicine, Physician, Vice Chancellor, University of Health Sciences, Lahore.
02	Prof. Brig. (R), Muzammil Hassan Najmi.	Professor of Pharmacology, Foundation University, Islamabad.
03	Prof. Nadeem Irfan Bukhari.	Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore.
04	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. Member CSC.
05	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi Co-opted Member.
06	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
07	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.
08	Miss Zaeba	Representative of PPMA

4. Chairman, CSC welcomed all the members. He briefed the members regarding this emergency meeting agenda. Chairman, CSC also thanked members for their active participation online through Zoom.

5. Meeting started with the recitation of holy verses of the Quran by Dr. Abdur Rashid, Chairman CSC/ Director, Division of Pharmacy Services.

AGENDA ITEM - I:

DELIBRATION ON "RANDOMIZED, DOUBLE BLINDED, PARALLEL, PLACEBO CONTROLLED, PHASE-I CLINICAL TRIAL TO EVALUATE THE SAFETY & IMMUNOGENICITY OF INACTIVATED SARS-COV-2 VACCINE IN HEALTHY POPULATION AGED 18 & ABOVE"

1.1 The sole agenda is the deliberation of CSC on the following:

a - "The matter regarding Sinopharm's Covid-19 vaccine"

b - Comparison between Sinopharm's Covid-19 vaccine used in ongoing Phase-I trial, already approved by CSC, being conducted in Pakistan & Phase-III Clinical Trial conducted in U.A.E.

c - The matter of Emergency Use Authorization of Sinopharm's Covid-19 vaccine in U.A.E.

1.2 Brief on "RANDOMIZED, DOUBLE BLINDED, PARALLEL, PLACEBO CONTROLLED, PHASE-I CLINICAL TRIAL TO EVALUATE THE SAFETY & IMMUNOGENICITY OF INACTIVATED SARS-CoV-2 VACCINE IN HEALTHY POPULATION."

S.No.		
01	Investigational products:	Inactivated SARS-CoV-2 Vaccine.
02	Purpose of the trial/study:	To investigate the safety of the Inactivated SARS-CoV-2 vaccine after vaccination in healthy people aged 18 years & above.
03	Principal Investigator	Prof. Dr. Iqbal Choudhary, Director, International Center for Chemical & Biological Sciences (ICCBS), University of Karachi.
04	vaccine is developed by	M/s Beijing Institute of Biological Products Co., Ltd, China (a subsidiary of Sino Pharm, China) China National Pharmaceutical Group.
05	Clinical Trial Site	The Indus Hospital, Karachi.
06	Participating Countries.	Applicant claimed that trial will be carried out in following countries: China U.A.E Pakistan.
07	Trial Subjects in Pakistan	112 Subjects.
08	Recruitment status	56 (till 7th December 2020)
09	AEFI/ADR	Minor Headache, Mild Fever & Pain at site of injection.

1.3 Chairman CSC briefed regarding site & study approval as follows:

i. ICCBS, University of Karachi had been applied for approval to act as CRO on 8th February 2019, the premises was inspected on 15th, 16th & 22nd November 2019 by a five membered expert panel and after approval from CSC in its 6th meeting, held on 20th January 2020, license to act as CRO issued on 3rd February 2020.

ii. Indus Hospital, Karachi had applied for approval to act as Clinical Trial Site on 25th January 2019 & a five membered panel inspected the premises, inspection report presented before CSC in its 4th meeting held on 17th July 2020 CSC approved the Ghauri Clinic of The Indus Hospital, Karachi to act as a Clinical Trial Site and licence issued on 9th October 2019.

iii. Another application from The Indus Hospital was received to act as a Clinical Trial Site for a different clinical trial on 4th February 2020. Application placed before CSC in its 7th meeting held on 18th February 2020. CSC approved the site & licence issued on 20th February 2020.

iv. Application for approval of Phase-I clinical trial on COVID vaccine (developed by M/s Beijing Institute of Biological Products Co., Ltd, China (a subsidiary of Sino Pharm, China) China National Pharmaceutical Group.), was received from ICCBS, University of Karachi on 1st July 2020. Application placed before CSC in its 13th meeting held on 11th August 2020. CSC approved the Phase-I clinical trial on vaccine and registration letter issued on 24th August 2020.

v. Chairman CSC highlighted the concerns discussed in the NCOC & forwarded by CEO-DRAP regarding Sinopharm's **Inactivated SARS-Cov-2** Vaccine & grant of Emergency Use Authorization (EUA) after completion of phase-III clinical trial in UAE.

vi. Chairman CSC also informed that for Emergency Use Authorization (EUA) in Pakistan a committee of experts under Chairmanship of Prof. Brig. (R) Muzammil Hassan Najmi has been constituted and the Chairman CSC is also co-opted member of that committee. The committee is mandated to evaluate the data of clinical trials of Covid vaccines for registration in Pakistan.

1.4 CSC members deliberated the matter and discussed as follows:

I. <u>Prof. Dr. Javed Akram:</u>

i. Prof. Dr. Javed Akram discussed the matter & raised concerns that by only verbal communication it is difficult to understand NCOC concerns. So, in best public/committee interest it is suggested that the trial may be halted for one week & NCOC may requested to submit concerns in writing so the matter may be discussed/addressed accordingly. He also said that written communication of concerns is also a legal formality for CSC to act accordingly.

ii. Prof. Dr. Javed Akram informed the members that development of a vaccine is a difficult task & may take 5 to 7 years. Clinical study is done in a linear way. First, of all lab work is performed then animal study is conducted then the Phase-I, II & III trials are carried out on humans & it takes 5-7 years. But during pandemic various clinical trials being conducted all over the world and all the process of vaccine development is being compressed and all over the world phase-I /II or III are started simultaneously without waiting for phase-I/II results due to medical emergency/pandemic situation.

It is an emergency condition; daily thousands of peoples are dying globally so the scientists can't wait for bureaucratic procedures. There is also a risk but for development of vaccine in this pandemic situation risk may be taken in best public interest.

iii. He suggested that as NCOC, the leading body for the pandemic has raised concerns on the Phase-I trial of the Sinopharm's **Inactivated SARS-Cov-2** Vaccine so in the best interest of the committee the trial may halted for one week & NCOC may requested to provide its concerns in writing within a week, so the committee can address/discuss accordingly in its next meeting. Prof. Dr. Javed Akram requested all members for appraisal of his suggestion as decision & if members are not agreed upon then it will his dissenting note.

iv. He requested that after NCOC concerns have been received in written form then latest update regarding the trial approval, enrollment, and ADR data may be forwarded to all CSC members, so the committee could decide stop the trial or to allow the continuation of trial in the next meeting.

v. He also suggested that the CSC may constitute a two membered sub-committee for inspection of the trial site for analyzing trial status & trial data. He also suggested that the data & concerns raised by the NCOC may also be shared with NBC-PHRC for opinion.

vi. Chairman CSC asked the opinion regarding conflict of interest & whether different trials may carried out on the same site or not, Prof. Dr. Javed Akram replied that there is no conflict of interest to conduct different trials on same site and a principal investigator may participate in different clinical trials as a co-principal investigator. In his opinion there is no conflict of interest. He also suggested that committee may ask from all principal investigators & research associates of approved trials to submit non-conflict of interest in financial matter with the sponsor.

II. Dr. Aamir Jaffary:

i. Dr. Aamir submitted that interim data for Phase-I trial of the Sinopharm's **Inactivated SARS-Cov-2** of 56 subjects has been received by NBC-PHRC in last week and till date no Serious Adverse Event (SAE) is reported.

ii. Further he said that if we have not enough information regarding NCOC concerns so why the meeting is being carried out. So, it is again suggested that NCOC may be asked for its concerns in written form, so the committee address accordingly.

III. Prof. Brig. (R), Muzammil Hassan Najmi.

i. Prof. Brig. (R), Muzammil Hassan Najmi briefed the committee regarding the issues/concerns of NCOC, as communicated by the CEO DRAP. He informed the committee that there are two different vaccine trials approved by the CSC in Pakistan, one is mRNA-based vaccine (developed by M/s CanSino Biological product, China) for which NIH is authorized to conduct phase-III clinical trial in Pakistan at six different clinical trial sites. Whereas another vaccine **Inactivated SARS-Cov-2 is a** killed virus vaccine for which ICCBS, University of Karachi is authorized to conduct trial at the Indus Hospital, Karachi. So, both different vaccines may not be confused with each other. There are no concerns raised about the vaccine developed by M/s CanSino Biological product, China and there is no problem in carrying out both vaccine trials at the Indus Hospital, Karachi.

ii. The main concern raised by the NCOC is on the Phase-1/2 trial of **Inactivated SARS-Cov-2** vaccine**.** As the data of the Phase-III trial (conducted on 50000 subjects) is

available now and a committee has already been constituted for evaluation of the data, so the concern is that if data of 50000 subjects in the phase-III trial is available so why we are still conducting a phase-I clinical trial of 112 subjects. Secondly, it's a regulatory dilemma that if we are conducting phase-I trial of a vaccine, how emergency use authorization can be granted to that vaccine. And these are the main two concerns to be focused on.

iii. He said that in his opinion a scientific justification for phase-I/II trial on inactivated vaccine may be present, because every population has its own ethnicity and genetic composition of population which may result in a different response to the drug and since data of 50000 subjects of phase-III clinical trial is not on Pakistani population so there is a reason or justification for conducting phase-I trial on Pakistani population. But to remove regulatory dilemma or any technical hitch if it is necessary to stop phase-I clinical trial of the vaccine before granting EUA, the bodies/departments involved in the phase-I/II clinical trial may request to change the objective of their study and may not call it a phase-1 trial. The study can be carried out to look for safety of the vaccine in Pakistani population on the basis of pharmacogenetics. That will remove the technical hitch for grant of EUA for the vaccine.

iv. Alternatively, he suggested that the PIs of the Phase-1 trial in Pakistan may be informed that Phase-3 clinical trial data of the same vaccine has become available and officially shared with Pakistani authorities and they may be requested to voluntarily stop the Phase-1 trial in this changed scenario.

v. Chairman CSC agreed with opinion of Prof. Brig. (R), Muzammil Hassan Najmi, Dr. Aamir Jaffrey added that it is correct that there is no justification Phase-1 trials when Phase-3 has already been completed and therefore the trial should be terminated. Prof. Dr. Javed Akram added that he agrees with justification but suggested that the committee should not decide for the termination it should wait for data from NBC-PHRC & concerns of NCOC in written afterwards the decision for termination of the phase-I trial may be decided in next meeting, at the moment trial may halt for further enrolment for one week.

IV. Dr. Rizwana Chaudhry:

i. Dr. Rizwana Chaudhry asked the members that it is a very important question that if the phase-III trial is of the same vaccine so why manufacture/sponsor get phase-I trial approval in Pakistan. Chairman CSC replied that the question was already asked from the applicant, as at the time of application there was no data was available so sponsor simultaneously applied at different sites for phase I, II & III clinical trials. Dr. Javed Akram added that at that time there was a need of phase-I clinical trial & at that time phase-III trial was not started, now as the phase-III trial data is available so the committee review the need of phase-I trial in the Pakistan after receipt of in written concerns, and after receiving of data submitted by inspection committee the committee should analyze accordingly. Dr. Rizwana added that is there any need of such inspection? Prof. Nadeem Irfan added that there is no need of such inspection, the committee should rely on submitted data & concerns, inspection may delay the process.

V. Dr. Farhana Badar:

i. Dr. Farhana Badar added that she agrees with all honorable members that in written concerns may get to see what it is actually about and what are the concerns of NCOC

and should be addressed accordingly by investigators & the committee. Chairman CSC briefed regarding clinical trial site approval of the Indus Hospital & ICCBS as a CRO. Further Chairman CSC added that as suggested by members of the committee a two membered panel may inspect the Indus Hospital, Karachi and suggested that Prof. Brig. (R) Muzammil Hassan Najmi or Prof. Dr. Javed Akram may inspect the premises and he is also available or Dr. Aamir Jaffrey may be part of the panel. Prof. Dr. Javed Akram suggested that Chairman CSC along with Prof. Brig. (R) Muzammil Hassan Najmi inspect both the CRO and sites of the phase-I vaccine trial and share report & data to all members two days before the next meeting so the member go through the data and submit their input for decision addressing the concerns of NCOC. Prof. Brig. (R) Muzammil Hassan Najmi added that as Chairman already informed that the CRO & sites inspected by the expert panel and further clarify that NCOC has not concerns regarding technicalities of approval so there is no need of reinspection. Prof. Brig. (R) Muzammil Hassan Najmi clarify again that the main concern of NCOC is that if there is data available for phase-III and also provided to Pakistan, so what is the need/justification for phase-I clinical trial concerns also raised on the working of CSC that when phase-I approval was granted at that time is there anything in record about phase-III trial approval. If CSC was aware of phase-III approval so it should be counted as mistake and it is an international scenario so all things may not be in knowledge of the committee and decision were taken on war footing. It is also agreed that concerns of NCOC regarding phase-I clinical trial are not provided in written. Brig. (R) Muzammil Hassan Najmi informed that he was present in evaluation committee and CEO-DRAP who attended the meeting of NCOC and he informed regarding the concerns of NCOC, on that basis he trying to all members of CSC & if CSC members are on the same point for in written concerns so the NCOC may also requested for that, this meeting also called to save the time so the EUA may granted. Second meeting of the evaluating committee will be held on Monday 28th December 2020, and after evaluating data it will be forwarded to registration board for emergency use authorization of Inactivated SARS-Cov-2 (killed) vaccine. Brig. (R) Muzammil Hassan Najmi further informed that, NCOC taking measure to expedite the process of EUA, as China used the vaccine for their army so why we are still conducting phase-I clinical trial for one hundred subjects.

1.5 Chairman CSC informed the members that, Prof. Dr. Raza Shah (Co-PI) also available and committee should give a chance for personal hearing before taking any legal action.

1.6 Prof. Dr. Raza Shah called before the committee to brief their point of view regarding conduct of phase-I clinical trial. Prof. Dr. Raza Shah joined the meeting and informed all members that the Indus Hospital Karachi is one of the sites at which both phase-I & phase-II trials of the covid vaccine are ongoing. The Indus Hospital Karachi has arranged two completely separate setups for both trials and two different teams are deputed for these trials, even two separate premises were arranged for these two different trials and so both trials are completely isolated from each other and there is no chance of intermixing of staff or facilities. Further QA Section of ICCBS is also closely monitoring the phase-I clinical trial of Inactivated SARS-Cov-2 vaccine, so there is no conflict of interest and it is usual that internationally an organization may involve in more than one clinical trial in parallel and the Indus Hospital has the capability to conduct more than one clinical trial. Further Prof. Dr. Raza Shah informed that as it is a double-blind trial, so they don't know about the volunteers that who get the vaccine & who get placebo, ICCBS started the trial from end of October 2020 after getting shipment of vaccine, there was two cohorts, cohort-I was for healthy volunteers of age below 60 years & cohort-II was for healthy volunteers of age above 60 years. Cohort-I is easily completed because in Pakistan it is easy to enroll health volunteers below 60 years of age, Cohort-II is also in progress and in next couple of weeks will

be completed. Till date no Serious Adverse Events are reported, most commonly ADRs reported during the trial were mild fever & pain at injection site

1.7 Dr. Rizwana Chaudhry added that, at the moment we are not discussing the ADRs/SAEs, we are discussing that if a phase-III trial is completed so why we still conducting phase-I clinical trial or is there any reason/justification for conducting a phase-I clinical trial? as after completion of phase-III clinical trial vaccine got EUA so there is no need of phase-I clinical trial. Dr. Rizwana Chaudhry also raised concerns on the manufacturer/sponsor that if the vaccine is same for which phase-III trials already completed and EUA granted so why not sponsor itself halted the phase-I clinical trial. Dr. Raza Shah replied that, at the time they were going to conduct phase-I clinical trial there was no phase-III trial for the vaccine was in progress and process to conduct phase-I clinical trial in Pakistan was initiated in April 2020. Now there is an explosion of data regarding vaccine but in previous months there was no credible data available to go for directly for phase-III clinical trial in Pakistan, phase-III trial initiated after the phase-I clinical trial. Secondly there was no available data on population for phase-I vaccine trial, so they decided instead to go for a phase-III trial on a vast population of Pakistan its safety should be checked through a phase-I clinical trial on our population. Further when Chinese company contacted the ICCBS the firm informed that their phase-I/II trials are in progress and there was no phase-III approval so ICCBS also agreed to conduct phase-I/II trial in Pakistan.

1.8 Dr Rizwana Chaudhry again asked that as phase -I was initiated in April 2020 or July 2020 but after completing the phase-III trial in other part of the world so why sponsor have not withdrawn their phase-I trial. Prof. Dr. Raza Shah replied that sponsor have not withdrawn the trial because there was no data regarding safety in Pakistani population. Dr. Rizwana replied that so it should be called safety testing on Pakistani population it should not be called a phase-I trial, Chairman CSC added that so it should be a safety trial rather than a phase-I clinical trial.

1.9 Prof. Dr. Raza Shah clarified that the trial has two outcomes, primary outcome is safety whereas immunogenicity is secondary outcome. Chairman CSC asked Prof. Dr. Raza Shah that if we suggest as phase-III trials are completed & EUA granted, if the committee suggest converting this trial to safety profile study on Pakistani population would you agree? Prof. Dr. Raza replied that, there are many organizations like ICCBS, Sinopharm & Board is involved, and it is an international study and there are international agreements so it is not in his mandate to agree and requested that phase-I trial should allowed to continue as it is, because for this trial there are many efforts and soon the trial will be completed, and within 2-3 weeks after analyzing the data of interim results they will submit its report. Chairman CSC replied to Prof. Dr. Raza informed that all the members noted the point of view from ICCBS whereas there are provisions in the rules and final decision will take according to law.

1.10 Dr. Rizwana added that it is not the committee decision to inspect the trial premises, the topic of discussion is that the committee granted phase-I approval of the trial, whereas phase-III trial is completed so the committee should decide whether phase-I trial allowed to continue or to stop that trial, as half of the recruitment done till date and it is not possible to recruit remaining subjects and complete the study within two weeks and results of phase-III trials are available so there is no need of phase-I trial of the same vaccine. Dr Aamir Jaffary agrees with Dr. Rizwana and stated that, there is no moral justification for recruiting the subjects for phase-I trial of a vaccine for which phase-III trial is completed & vaccine got approval and if the vaccine is required for our country so how we can allow phase-I clinical trial while phase-III already done, it should also consider by Sinopharm itself that if they conducted phase-III trial so why they are conducting phase-I trial in our country.

1.11 Dr. Mushtaq Ahmed added that people of Pakistan taken so lightly, it is not a way that after conducting phase-III trial in other countries afterwards we are invited to join in that trial, if there is data came from rest of the world is sufficient so there is no need to conduct phase-I/II trials in Pakistan. Secondly it is a scientific body so we should not arbitrarily jump to the conclusions and he agrees with Dr. Javed Akram that until the data is not received in black & white, we should not make the decisions,

because we are accountable for all decision taken by the committee, so committee should wait for data for 3 to 4 days until that the committee should not take any decision, thirdly whenever any study approved on monthly basis data should be submitted to the DRAP. Madam Farhan Badar added that Sinopharm should also explain regarding the matter, Chairman CSC replied that at the time no representative is present here from Sinopharm, applicant is available, and the committee heard applicant's point of view. Dr. Farhana Badar again added that recruitment is so slow, and it is a very strange situation that in six months only 60 subjects recruited.

1.12 Chairman CSC asked all members for any comments before conclusion. Prof. Brig. (R) Muzammil Hassan Najmi added that he agrees with Dr. Rizwana Chaudhry & Dr. Aamir Jaffrey, Chairman CSC requested to repeat the suggestion so we prepare the draft minutes and will share with Prof. Brig. (R) Muzammil Hassan Najmi and after agreeing then the draft will be shared with remaining members. Prof. Brig. (R) Muzammil Hassan Najmi submitted that the crux of all discussion is that, after conclusion of the phase-III clinical trial there is no justification for phase-I clinical trial and if the committee granted approval for the phase-I trial at that time due to it was not in the knowledge of the committee that there is also a phase-III trial is approve or being approved for the same vaccine so now after completion of the phase-III clinical trial of the vaccine data is forwarded/handed over to us officially, so the Principal Investigators conducting phase-I trial in the Pakistan may be requested for voluntarily stop the phase-I trial of the vaccine and it is the simplest solution to this problem. Chairman CSC agrees with Prof. Brig. (R) Muzammil Hassan Najmi and stated that we will prepare the draft will share with Prof. Brig. (R) Muzammil Hassan Najmi and if Principal Investigators of the phase-I trial will not withdraw from the trial so then the committee will take regulatory decision and applicant may also asked for option to continue as safety profile/parameter study. Further Chairman agrees that when there is phase-III trial is completed there is no need of phase-I clinical trial of the same vaccine.

1.13 Dr. Rizwana Chaudhry added that basically the trial should be withdrawn by the sponsor, as it is a very important question, as sponsor/manufacturer was known of whole scenario and as phase-III trial is completed and phase-I is progressing very slowly so the sponsor itself should withdraw from the phase-I trial. Prof. Dr. Javed Akram added that all the member discussed the matter very well and requested Chairman CSC that on behalf of CSC, CEO-DRAP requested to provide point wise concerns in written and then shared with all CSC members for preparation, meanwhile interim result shared from the trial site should also be provided, so the members may evaluate concerns of NCOC so addressed accordingly and trial may halt for one week so the member can understand the concerns and then take decision accordingly.

1.14 Chairman CSC concluded the meeting and as per all above discussion CSC decided as follows:

Decision of 18th CSC meeting:

The CSC after detailed deliberation and owing to situation of COVID-I9 pandemic in Pakistan in order to protect the patients, decided as follows:

i. *CSC decided to forward a request to NCOC for sharing its concerns regarding Phase-I clinical trial on Sinopharm Vaccine in writing so that the CSC could deliberate, discuss & dispose the matter accordingly.*
ii. *The CSC decided that PI of the Phase-I clinical trial of Sinopharm Vaccine may be asked for withdrawal of the trial voluntarily as after completion of the Phase-III clinical trial and use on large scale in Chinese Armed Forces and grant of emergency use authorization in U.A.E. there is no need to continue Phase-I clinical trial of the same vaccine in Pakistan.*