Minutes of 1ST Meeting of Clinical Studies Committee, held on 7th February 2019 in University of Health Sciences, Lahore

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Minutes of 1ST Meeting of Clinical Studies Committee held on 7th February 2019.

The first meeting of the Clinical Studies Committee (CSC), DRAP was held on 7th February 2019 in the Senate Hall of University of Health Sciences (UHS), Lahore and the following attended the meeting:

Sr. No.	Name	Designation
1.	Mr. Ghulam Rasool Dutani	Chairman CSC / Director Pharmacy Services
2.	Dr. Masud ur Rehman	Secretary CSC / Additional Director Pharmacy Services
3.	Prof. Dr. Javed Akram	Member (Medical Specialist) / Vice Chancellor UHS
4.	Prof. Nadeem Irfan Bukhari	Member (Professor of Pharmacy) / Principal PUCP
5.	Ms. Faiza Bashir	Member (Nominee Executive Director-PHRC) / National Coordinator NBC
6.	Dr. Farhana Badar	Member (Statistician) / Biostatistician & Cancer Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Centre
7.	Dr. Ahmed Nawaz	Observer (Pharma Bureau Representative) / Medical Director Pfizer

Ms. Aqsa Hashmi (AD, Pharmacy Services) also attended the meeting and assisted Dr. Masud ur Rehman (Secretary CSC) with agenda of the meeting.

Meeting started with recitation of the Holy verses. The Chairman CSC welcomed all the members and participants of the meeting.

The Chief Executive Officer, DRAP, Mr. Sheikh Akhter Hussain, also participated in the meeting. The CEO gave a brief note on the discussion during the hearings of Constitution Petition No.73 of 2018 of the Supreme Court Pakistan. He briefed the Committee on each point of the direction of the case. He afterwards highlighted the importance of this newly notified CSC and the need to regulate clinical research in Pakistan. The CEO also informed the members of the Committee that, fee notification under the Bio-study Rules 2017 has been approved by the Authority and the fee structure is placed for approval of the Policy Board in the very next meeting.

Prof. Dr. Javed Akram member CSC/ Vice Chancellor UHS, gave a presentation on Clinical Research & Guidelines from Test Tubes to Patients (A Journey through Discovery of Medicine). The presentation was appreciated by all the participants.

The agenda items were discussed as follows:

AGENDA ITEM NO. I: MISCELLANOUS CASE.

1) Coopt Member for Stem Cell Research as Per Direction of Hon'ble Supreme Court.

Hon'ble Supreme Court of Pakistan, while disposing the case under Constitution Petition No.73 of 2018 regarding the "Mechanism to Commercialize Research Breakthrough" order on 15th January 2019, to the concerned quarters for the implementation of the court decision on their part. In this regard, CSC was directed to co-opt Prof. Dr. Sheikh Riaz-ud-Din as its member to avail benefit of his expertise under clause (j) of Rule.13 (1) of the Bio-Study Rules, 2017.

Decision: In compliance to the order of the Supreme Court of Pakistan, the Committee co-opted Prof. Dr. Sheikh Riaz-ud-Din as member of CSC, to avail benefit for his expertise.

2) Development of Guidelines for Stem Cells/Cells Research Guidelines by the CSC as per direction of Hon'ble Supreme Court of Pakistan.

The Hon'ble Supreme Court of Pakistan, while disposing the case under Constitution Petition No.73 of 2018 regarding the "Mechanism to Commercialize Research Breakthrough" order on 15th January 2019, to the concerned quarters for the implementation of the court decision on their part. In this regard, CSC was directed to develop stem cells / cells research guideline within a period of three months.

Discussion: Dr. Faiza Bashir (National Coordinator of National Bioethics Committee NBC-Pakistan Health Research Council PHRC) informed the committee that NBC-PHRC has a guideline, already drafted and uploaded on the official website **http://nbcpakistan.org.pk/guidelines.html**.

Dr. Sheikh Riaz-ud-Din (Head CEMB/CAMB Lahore) briefly highlighted the importance of Stem Cell therapy and the inclusion of the same in the Bio-Study Rules 2017 for advancement in clinical research. Dr. Javed Akram pointed out that stem cell products are still being researched on, and the matter needs to be considered before making any amendments in the rules. Dr. Masud ur Rehman added that internationally stem cells and other advanced therapies are being regulated as Advanced Medical Research Therapies (AMRT) and respective regulation in Pakistan may be made accordingly.

Decision: CSC constituted a subcommittee including Dr. Javed Akram, Dr. Sheikh Riaz-ud-Din, Dr. Masud ur Rehman, Dr. Faiza Bashir, to review the Stem Cell guidelines of NBC-PHRC and submit report to CSC within fortnight. On recommendation of Dr. Sheikh Riaz-ud-Din, Dr. Moazzam Tarar (MBBS, FRCS, FCPS (Plastic Surgery) Jinnah Hospital Lahore) was also included in the sub-committee due to his expertise in the stem cell research.

AGENDA ITEM NO. II: LICENSING OF CRO, CLINICAL TRIAL SITE AND BA/BE CENTRE UNDER BIO STUDY RULES, 2017

Discussion Agenda Item No II: The Committee was informed that some of the cases under Agenda item II, were complete and were awaiting the notification of fee under the Bio-study Rules 2017 by the Policy Board, DRAP. The Committee was also briefed that the case of "Notification of fee under the Bio-study Rules 2017", has been approved by the Authority in its 62nd meeting and is now awaiting approval of the Policy Board.

The Chairman also pointed out that a panel inspection may be conducted before approval of the CROs, Clinical trial sites, BE/BA Centres and clinical research laboratories.

Dr. Javed Akram volunteered the services of UHS, for collecting CVs of Professionals from healthcare sector, with experience in clinical studies, which may then be sent to DRAP for selection by the Chairman CSC and CEO DRAP, to make a national pool for inspection purposes. DR. Javed Akram also proposed that the UHS may help in conducting training session of the selected individuals on inspection of CROs, Clinical trial sites, BE/BA Centres and clinical research laboratories. Mr. Nadeem Irfan Bukhari also volunteered his services for being part of the inspection panel.

Cases for licensing of Clinical studies centers, BA/BE Studies Centers, CRO and Bio-Lab applied on **Form-I** under the **Bio-Study Rules 2017** were decided as under:

1) M/S DRK Pharma Solutions (Pvt) Ltd, For CRO, F.3-13/2017.

Application is from Azam Shahid Jafri, Director Commercial and Operation, M/s DRK Pharma Solutions (Private) Ltd., 15 KM Multan road, Lahore dated 3rd October 2018, to work as Clinical Research Organization.

After evaluation some observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **12-12-2018**, Firm replied as following:

Summary of reply against observations are as follow:

S.No.	Observations	Comments / Reply
1	The firm is applying for license of both CRO and Clinical Trial Site, However, for each category a separate application is required.	We as the subject specifies have applied only for CRO. As given above in the "*Independent ethics committee (IEC)"* definition and explanation IEC is responsible to ensure the protection of the rights, safety and well-being of human subjects involved in a trial protocol and to provide public assurance of that protection by among other thing, reviewing and approving or providing favorable opinion on the trial protocol, the suitability of the investigators, facilities, methods and material to be used in obtaining and documenting informed consent of the trial subjects.
2	Details of premises including layout plan not provided.	The layout plan of our office has been attached as Annex 3.

3	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies is not provided.	We shall not be required to do these as sponsor of clinical trial Phase II, III and IV. These are required by Bioequivalence centers and for Phase-I trials. As per our application on Form-I (attached) we have applied for organizing and monitoring Phase II, III and IV.
4	Names and qualifications of the section wise staff not provided.	The document attached as Annexure 2, contains the CVs of the employees required for conduct of clinical trial and monitoring.
5	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling not provided.	The trial sites to be monitored by us are hospitals which has all the facilities required for any emergency and is reviewed and approved by IEC.
6	Deposited fee will be adjusted after notification by the Authority.	Shall be done as required.

After submission of reply and clarification regarding observations, it is clear that the applicant firm only work as CRO and provide services to conduct clinical trial, and not conduct clinical trial itself.

After scrutiny status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	In recent submission "CRO" is ticked.	--
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	Yes	--
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	As per reply Not applicable as they will not conduct any studies.	--
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	As per reply Not applicable as they will not conduct any studies.	--

9	Undertaking	Provided on stamp paper.	--
10	Prescribed Fee	Rs.50000 submitted.	--

Following deficiencies were identified:

i) Submission of fee pending as per approval and notification by Policy Board DRAP.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority. The CSC also decided to inspect the CRO, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

2) M/s Pioneer Research Solutions (Pvt) Ltd, For CRO, F.3-5/2017(Old) F.15-3/2017(New)

Application is from Tanweer Ahmed CEO, Pioneer Research Solutions (Pvt.) Ltd, House No. 20 St. No.29, Sector F-8/1 Islamabad dated 20th April, 2017, to work as Clinical Research Organization.

After evaluation following observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **12-12-2018**, and three reminders also sent on **7th,11th and 28th January, 2019**, but still response is awaited.

After scrutiny status of application is as follows

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	--	Not Provided
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	--	Application is not on prescribed Form-I.
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	--	Not Provided

6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	--	Not Provided
7	Names and qualifications of the above sections along with their staff.	--	Not Provided
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	--	Not Provided
9	Undertaking	--	Not Provided
10	Prescribed Fee	--	Not Provided

Description of shortcomings:

Following deficiencies were identified:

i) Application is not on prescribed Form-I of the Bio-Study Rules 2017.

ii) Submission of fee pending as per approval and notification by Policy Board DRAP.

ii) Undertaking on stamp paper is not provided.

iv) Details of premises including layout plan not provided.

v) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies is not provided.

vi) Names and qualifications of the section wise staff not provided.

vii) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling not provided.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority and to complete all the deficiencies in the application. The CSC also decided to inspect the CRO, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

3) M/s Pharma Professional Services (Pvt) Ltd, For the License of BA/BE Centre F.No. 15-1/2018 DD (PS)

Application is from Prof. Dr. Tasneem Ahmed, CEO, Pharma Professional Services (Pvt.) Ltd, A-93 Ettawah society, Ahsanabad, [near Gulshan-e-Maimar], Gadap Town, Karachi, wherein the request has been made to register their company with DRAP as BA/BE Studies Center and Clinical Research Organization (CRO), dated 18th October, 2018.

After evaluation observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **07-01-2019**, and reminders were also sent on **11th and 23rd January, 2019**. The firm in its recent communication dated 26th January, 2019 submitted application on Prescribed

Form-I for the BA/BE Centre, dully singed and stamped by the firm along with fee and undertaking on stamp paper.

After scrutiny the status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	As per the most recent submission, application is submitted on Form-I for BA/BE Centre	--
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	Yes	--
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Yes	--
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Yes	--
9	Undertaking	Yes	--
10	Prescribed Fee	*Fee of 20,000 has been submitted on one challan for both Clinical trial site and BE/BA Centre.	

Description of shortcomings:

Following deficiencies were identified:

i) Submission of fee pending as per approval and notification by Policy Board DRAP.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority. The CSC also decided to inspect the BA/BE Centre, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

4) M/s Pharma Professional Services (Pvt) Ltd, For the License of Clinical Trials Site F.No. 15-4/2019 DD (PS)

Application is from Prof. Dr. Tasneem Ahmed, CEO, Pharma Professional Services (Pvt.) Ltd, A-93 Ettawah society, Ahsanabad, [near Gulshan-e-Maimar], Gadap Town, Karachi, wherein the request has been made to register their site with DRAP as Clinical trial site dated 15th January, 2019.

After evaluation observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **23-01-2019**. The firm accordingly on 26th January, 2019 has submitted the application on Form-I, duly stamped and signed along with undertaking and fee.

After scrutiny the status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S. No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	Applied on Form-I.	--
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	Yes	--
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Yes	--
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Yes	--

9	Undertaking	Provided	
10	Prescribed Fee	*Fee of 20,000 has been submitted on one challan for both Clinical trial site and BE/BA Centre.	

Description of shortcomings:

Following deficiencies were identified:

i) Submission of fee pending as per approval and notification by Policy Board DRAP.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority. The CSC also decided to inspect the Clinical Trial Site, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

5) M/s Metrics Research (Pvt) Ltd, For CRO & SMO and Clinical Trial Site, F.3-7/2018

Application is from Syed Muhammad Iftikhar Zaidi, CEO Metrics Research (Pvt) Ltd, Plot No. 23-C, 3rd Floor, Old Sunset Boulevard, DHA Phase-II, Karachi, dated 10th September, 2018, wherein the request has been made for license of their company with DRAP to work as Clinical Research Organization (CRO) and Clinical Trial Site

After evaluation observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **12-12-2018**, and **two reminders also sent on 09th and 28th January, 2019**, but still response is awaited.

After scrutiny the status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	Nothing ticked on Form-I.	--
4	Particulars regarding the legal status of the applicant	Yes	--

5	Details of premises including layout plan of the site	--	Not Provided
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	--	Not Provided
7	Names and qualifications of the above sections along with their staff.	Provided	
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	--	Not Provided
9	Undertaking	--	Not on stamp paper
10	Prescribed Fee	--	Not provided

Description of shortcomings:

i) Application to issue license for CRO and Clinical Trial Site is submitted on same application without fee.

ii) Details of premises including layout plan of the clinical trial site is not provided.

iii) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies not provided.

iv) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling not mentioned.

v) Undertaking should be on stamp paper.

vi) Fee not provided.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority and to complete all the deficiencies in the application. The CSC also decided to inspect the CRO, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

6) M/s Dimension Research CRO & SMO, For and Clinical Trial Site, F.11-2/2018-DD (PS

Application is from Muhammad Khurram Zaki Khan, CEO of M/s Dimension Research CRO & SMO, Gulistan-e-Jauhar, Scheme-36, Karachi, Pakistan, dated 6th of August, 2018, wherein the request has been made for license of their company with DRAP to work as Clinical Research Organization (CRO) and for management service provider for Clinical Trial Sites.

After evaluation observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **12-12-2018**. The firm accordingly submitted some documents. In addition, two **reminders also sent on 11th and 28th January**, 2019, but still response is awaited.

After scrutiny status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	Both CRO and Clinical Trial Center are Ticked. But the Firm in response letter confirmed it is a "CRO".	--
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	As per reply Not applicable for the services they are offering.	Not Provided
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	As per reply Not applicable for the services they are offering.	Not Provided
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	As per reply Not applicable for the services they are offering.	Not Provided
9	Undertaking	Yes	--
10	Prescribed Fee	Rs.100000 Deposited.	--

Description of shortcomings:

Following deficiencies were identified:

i) Application to issue license for CRO and Clinical Trial Site on one application. However, in letter they confirm that it will be a CRO.

ii) Details of premises including layout plan of the clinical trial site is not provided.

iii) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies not provided.

iv) Details of the allied facilities associated with the trial center/CRO including ambulatory services, emergency handling not mentioned.

v) Submission of fee pending as per approval and notification by Policy Board DRAP.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority and to complete all the deficiencies in the application. The CSC also decided to inspect the CRO, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

7) M/s Pakistan Drug Testing & Research Center (PDTRC), For Bio-Lab, F.15-2/2018-DD (PS)

Application is from Dr. Shafiq-Ur-Rehman Chief Operating Officer, Pakistan Drug Testing and Research Center (PDTRC), Commercial Area (North), Sundar Industrial Estate, Sundar- Raiwind Road, Lahore dated 22nd October, 2018, wherein the request has been made to register their Lab with DRAP as Clinical Research Lab / Analytical Lab, wherein the request has been made to register their Lab with DRAP as Clinical Research Lab / Analytical Lab.

After evaluation observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **08-01-2019 and subsequent reminder also sent on 28th January, 2019**, but still response is awaited.

After scrutiny the status of application is as follows:

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable) (i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	Laboratory	--
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	Yes	--
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Yes	--
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	As per reply Not applicable.	Not Provided
9	Undertaking	--	Not Provided
10	Prescribed Fee	--	Not Provided

Description of shortcomings:

Following deficiencies were identified:

i) Scope of lab is not described properly, as the lab previously was working as third-party drug testing lab, it should be properly mentioned that under the Bio-Study Rules which services provided by the lab.

ii) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling not provided.

iii) Fee is not submitted.

iv) Undertaking on stamp paper is not provided.

v) Submission of fee pending as per approval and notification by Policy Board DRAP.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority and to complete all the deficiencies in the application. The CSC also decided to inspect the Bio-Lab, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

8) M/s Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, For CRO, Clinical Trial Site and BA/BE Studies Center. F.1-11/2010

Application is from Prof Dr. Muhammad Iqbal Choudary, Director, CBSCR-International Centre for Chemical and Biological Sciences, University of Karachi, dated 19th September, 2018, wherein the request has been made for license of their Centre with DRAP to work as Clinical Research Organization (CRO), Clinical Trial Site and BA/BE studies Centre.

After evaluation following observations were communicated as per prerequisites of prescribed **Form-I** of the **Bio-Study Rules 2017** on **12th December, 2018 and a reminder also send on 28th January, 2019** to submit separate application for each facility on form-I under the Bio-study rules, 2017 for CRO, Clinical Trial site and BA/BE Centre. However, no reply has been received so far.

After scrutiny status of application is as follows

Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017

S.No.	Prerequisites as per prescribed Form-I of the Bio-Study Rules 2017	Provided	Not Provided
1	Application on prescribed Form-I	Yes	--
2	Description regarding applicant and the firm	Yes	--
3	Type of the site meant for (whichever is applicable)	Firm has applied for CRO, Clinical Trial site and BA/BE	--

	(i) Bio-equivalence and Bio-availability studies (ii) CRO (iii) Laboratory (iv) Clinical trials- (a) Phase I (b) Phase II (c) Phase III (d) Phase IV	studies Centre on the same application	
4	Particulars regarding the legal status of the applicant	Yes	--
5	Details of premises including layout plan of the site	Yes	--
6	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Yes	--
7	Names and qualifications of the above sections along with their staff.	Yes	--
8	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Details of Facilities for first aid and emergency treatment for the staff and subjects are mentioned on one page and about the diagnostic lab, information technology and ambulatory services are mentioned on another page.	
9	Undertaking	--	Not Provided
10	Prescribed Fee	50,000PKRs submitted.	

Description of shortcomings:

Following deficiencies were identified:

i) Submission of fee pending as per approval and notification by Policy Board DRAP.

ii) Undertaking on stamp paper is not provided.

Decision: The Committee decided that the applicant be asked to submit fee which has been approved by the Authority and to complete all the deficiencies in the application. The CSC also decided to inspect the CRO, Clinical Trial Site and BE/BA Centre, through a panel of relevant experts approved by CEO, DRAP, after formation of National Inspection Pool.

AGENDA ITEM NO. III: CLINICAL TRIALS/STUDIES REGISTRATION

Discussion Agenda Item No III: The committee was informed that all the cases for registration of clinical trials under agenda item No III, were incomplete and applicants had not applied for licensing of their clinical trial sites.

The applications submitted for registration of Clinical trials/studies on **Form-II,** under the **Bio-Study Rules 2017** were collectively decided as under:

1) M/s ATCO Laboratories (Pvt) Ltd, for Clinical Trial on Aspirin, F.3-11/2018-DD(PS)

Application is from Maj. Amjad Farooq Butt (R) Manager Regulatory Affairs, ATCO Laboratories Limited Karachi, wherein request has been made for approval of Aspirin clinical trial, which will be carried out by Principal Investigator Prof. Javed Akram Vice Chancellor University of Health Sciences, Lahore and Dr. Muhammad Zaman Khan Co-Principal Investigator.

Application is containing only two pages, one letter is from Pakistan Aspirin Foundation in the name of Chairman ATCO Laboratories Karachi for provision of Enteric Coated Aspirin 75mg (Ascard 75mg) and Placebo Tablets, and another is an application on ATCO's Letter head in the name of Director Pharmacy Services for approval of said clinical trial.

After evaluation following observations were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017.

Following deficiencies were identified:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Not provided
2	Fee	Not provided
3	Investigator Brochure (s)	Not provided
4	Final protocol	Not provided
5	Informed consent and participant information sheet (Urdu to English)	Not provided
6	List of participating countries	Not provided
7	Phase of trial.	Not provided
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Not provided
9	Site approval of the trial and sites	Not provided
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Not provided
11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	Not provided

13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided
14	Pre-clinical/clinical safety studies	N/A
15	Summary of the Protocol	Not provided
16	Summary of the Investigator Brochure	Not provided
17	Adverse Event Reporting Form	Not provided
18	No of patients to be enrolled in each center.	49000 Patients, Details not provided
19	Name of Monitors & Clinical Research Associate	Principal Investigator: Prof. Javed Akram Co. Principal Investigator: Dr. Zaman Khan
20	Evidence of registration in country of origin.	Not provided
21	Evidence of registration in Pakistan.	Not provided
22	Sample of label of the investigational product / drug.	Not provided
23	Duration of trial	66 Months

The firm was communicated on 9th January, 2019 and subsequent reminder was also sent on 30th January, 2019 to apply on prescribed Form-I for Clinical trial Site approval and for Clinical Trial Studies on prescribed Form-II of the Bio-Study Rule 2017 along with all the prerequisites, but still response is awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

2) M/s Origin Pharma (Pvt) Ltd, for Clinical Trial on Insugin (Recombinant Human Insulin) 25IU Mouth rinse solution 5ml, F.3-08/2018-DD (PS)

Application is from Muhammad Farooq (MD), M/s Origin Pharma Pvt Ltd, 41-Baber Block, New Garden Town Lahore-Pakistan, for approval of Multicenter Observational Study For the drug Insugin (Recombinant Human Insulin) 25IU Mouth rinse solution 5ml, for clinical trial (Phase-III), East gate Pharmaceuticals Inc,2203-65, Harbour Square, Toronto Canada, Another application attached from Muhammad Farooq (MD),), M/s Origin Pharma Pvt Ltd, 41-Baber Block, New Garden Town Lahore-Pakistan, on Form-4 of rule 6 (30) of the Drugs (import & export) rules, 1976, For import of 2000 boxes of the drug for the study

After evaluation following observations were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017.

S. No.	Document	Remarks
1	Application on prescribed Form-II	Not provided
2	Fee	Not provided
3	Investigator Brochure (s)	Not provided
4	Final protocol	Not provided
5	Informed consent and participant information sheet (Urdu to English)	Not provided
6	List of participating countries	Not provided
7	Phase of trial.	Phase-III (Details not provided)
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	10*2000 Boxes
9	Site approval of the trial and sites	Anwar Riyaz-I-Qadeer Diabetes Institute Lahore. (Not approved yet by the DRAP)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Not provided
11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	Not provided
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided
14	Pre-clinical/clinical safety studies	Not provided
15	Summary of the Protocol	Not provided
16	Summary of the Investigator Brochure	Not provided
17	Adverse Event Reporting Form	Not provided
18	No of patients to be enrolled in each center.	200 Patients, Details not provided
19	Name of Monitors & Clinical Research Associate	Principal Investigator: Dr. Arif Riaz Qader
20	Evidence of registration in country of origin.	Not provided
21	Evidence of registration in Pakistan.	Not provided
22	Sample of label of the investigational product / drug.	Not provided
23	Duration of trial	66 Months

Following deficiencies were identified:

i) Application is for import of the drug for clinical trial, where clinical trial site and clinical trial is not approved from the DRAP.

ii) Application for clinical trial approval is not on prescribed form-II of the Bio-Study Rules 2017.

iii) Fee deposit slip is not attached.

iv) Prerequisite information as per form-II of the bio-Study rules 2017 are not provided.

v) The firm was advised to apply on prescribed form-I of the Bio-Study Rules 2017 for approval of Clinical Trial Site before applying for clinical trial approval.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

3) A Randomized Double-Blind, Clinical Trial on The Efficacy and Safety of "Yinhuang Qinfei Capsule" in The Treatment of Acute Exacerbation of Chronic Simple Bronchitis, F.3-5/2018-DD (PS)

Application is from Prof. M. Iqbal Chaudhary, Director, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, wherein request has been made for approval of "Clinical Trial On The Efficacy And Safety Of "Yinhuang Qinfei Capsule" In The Treatment Of Acute Exacerbation Of Chronic Simple Bronchitis", which will be carried out by Principal Investigator Prof. M. Iqbal Chaudhary and Dr. Kausar Aamir Co-Principal Investigator.

After evaluation following observations were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017.

Following deficiencies were identified:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Not provided
2	Fee	Not provided
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan and China.
7	Phase of trial.	Phase – II
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Not provided
9	Site approval of the trial and sites	Not provided

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Not provided
11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	Attached
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Valid GMP Certificate of M/s Hunan Anbang Pharmaceutical Co. Ltd., has been furnished.
14	Pre-clinical/clinical safety studies	Reports of animal studies are attached. However, no data regarding the Phase – I studies has been provided.
15	Summary of the Protocol	Attached
16	Summary of the Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Attached. 212 patients. (106 in each group)
19	Name of Monitors & Clinical Research Associate	Attached
20	Evidence of registration in country of origin.	Attached
21	Evidence of registration in Pakistan.	Not registered in Pakistan.
22	Sample of label of the investigational product / drug.	Attached
23	Duration of trial	12 Months

The firm was communicated that apply on prescribed Form-I for Clinical trial site approval and for Clinical Trial Studies on prescribed Form-II of the Bio-Study Rule 2017 along with all prerequisites, but response is still awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

4) Open Label, Non-Randomized, Multi-Center Investigator Initiated Study to Evaluate Effectiveness of Generic Velpatasvir and Sofosbuvir in Hepatitis-C with or without Ribavirin Among Pakistani Population, F.3-3/2018-DD (PS)

Application is from Prof. Dr. Syed Muhammad Zahid Azam, Dow University Hospital, Karachi, for approval of "OPEN LABEL, NON-RANDOMIZED, MULTI-CENTER INVESTIGATOR INITIATED STUDY TO EVALUATE EFFECTIVENESS OF GENERIC VELPATASVIR AND

SOFOSBUVIR IN HEPATITIS-C WITH OR WITHOUT RIBAVIRIN AMONG PAKISTANI POPULATION", Phase-IV clinical trial.

After evaluation following observations were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017.

The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Not provided
2	Fee	Rs.50,000 has been deposited as processing fee
3	Investigator Brochure (s)	Not provided. Prescribing Information of International brand of M/s Gilead Sciences, USA, has been furnished.
4	Final protocol	Attached Protocol Version 3.0,
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	The study is Pakistan specific only
7	Phase of trial.	Phase – IV Post – marketing observational study
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	1300 Packs, each containing 28 tablets of Velpatasvir/Sofosbuvir 100mg/400mg) Applicant has informed that the study drug will be provided by the M/s CCL Pharma, Lahore which has submitted that their product is pending for approval in Registration Division, DRAP. Whereas they have the registration of the same product for export purpose only and they can supply the same for study purpose. **Information regarding quantities and source of other trial material i.e Ribavirin has not been disclosed.**
9	Site approval of the trial and sites	Anwar Riyaz-I-Qadeer Diabetes Institute Lahore. Not approved yet.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Applicant has provided the approval of Institutional Review Committee, Dow University, Karachi.

11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	Attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	In-valid GMP Certificate of M/s CCL Pharmaceuticals (Pvt.) Ltd., has been furnished which has expired on 30-03-2018
14	Pre-clinical/clinical safety studies	Not provided
15	Summary of the Protocol	Attached.
16	Summary of the Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Attached. 30 to 40 patients at each site. **Total 300 Patients approximately.**
19	Name of Monitors & Clinical Research Associate	Attached
20	Evidence of registration in country of origin.	Not provided.
21	Evidence of registration in Pakistan.	Registration letter of Abriva Forte Tablet (Velpatasvir/Sofosbuvir 100mg/400mg) for Export Purpose, is attached.
22	Sample of label of the investigational product / drug.	Attached
23	Duration of trial	12 Months

Following deficiencies were identified:

i) Application for Clinical Trial Site approval on prescribed Form-I of the said rules and for approval of Clinical Studies to apply on prescribed Form-II.

ii) Product registration certificates used during Clinical studies not provided.

iii) Related to study title "Effectiveness of Generic Velpatasvir/Sofosbuvir…" license to manufacture drug for experimental purposes or drug registration certificate is required.

iv) Complete information regarding quantities and source of Zovirin is required.

v) GMP, CoPP and free sale certificate for the investigational products is required.

vi) Approval of National Bioethics Committee (PHRC) and Institutional Review Board of study sites is required.

The firm was communicated through letter no. F.No.3-3/2018 DD (PS), dated 06th June, 2018, after scrutiny of the reply another letter sent on 11th January, 2019, that apply on prescribed Form-I for

Clinical trial site approval and for Clinical Trial Studies on prescribed Form-II of the Bio-Study Rule 2017 along with all prerequisites, But still response is awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

5) Application of M/s Pharma Professional for Approval and Registration of Comparative Clinical Study of Irpo-Fa ® Tablets.

Application is from Professor Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and tolerability of combination tablets of Iron Polymaltose and Folic Acid of test product **Irpo-FA ® tablets** manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi compared with reference product **Maltofer Fol® tablets,** manufactured under license of M/s (Vifor International) Inc, in woman with Iron deficiency Anaemia(IDA) including pregnant woman.

2. The short summary of the proposed study is as under;

i. **Study title:** A comparative, open labelled, multicentre, double arm, controlled, and randomized study in iron deficient anaemic women including pregnant woman to compare the efficacy and tolerability of test product Irpo-FA ® tablets manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi with reference product Maltofer Fol® tablets, manufactured under license of M/s (Vifor International) Inc.

ii. **Investigational Product:** Irpo-FA ® (Iron Polymaltose and Folic Acid) tablets manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi.

iii. **Reference Product:** Maltofer Fol® (Iron Polymaltose and Folic Acid) tablets**,** manufactured under license of M/s (Vifor International) Inc.

iv. **Sponsor & Manufacturer:** M/s Nabiqasim Industries (PVT) Ltd, Karachi

v. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.

vi. **Study Sites:**

   a. Department of Gynaecology, JPMC, Karachi;

   b. Sobhraj Maternity Hospital Karachi; and

   c. Karachi Medical Complex.

vii. **Principal Investigator:** Dr. Haleema Yasmin.

viii. **Funding Source**: The sponsor

ix. **Cost of the Project**: 4,000,000 PKRs (approximately).

The details of the submitted documents as per checklist are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Application submitted as per Form-II of the Bio study Rules, 2017.
2	Fee	Not provided
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries if applicable	Conduct in Pakistan
7	Phase of trial.	Post-marketing study (Phase-IV).
8	Quantity of drug / trial material to be imported/ procured.	Reference Product: *Total 19380 tablets (14400 tablets for 80 subjects and remaining to be retained as per GCP standards).* Test Product: *Total 19380 tablets (14400 tablets for 80 subjects and remaining to be retained as per GCP standards).*
9	Site (s) of the trial.	a. Department of obstetrics and Gynaecology, JPMC, Karachi; b. Sobhraj Maternity Hospital Karachi; and c. Karachi Medical Complex. (All the three sites are not licensed by the DRAP neither the firm has applied for it.)
10	CVs of the Investigators	Attached
11	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval of trial and composition of the IRB provided; but the approval of the site by the IRB is not attached with application.
12	Approval of National Bio-ethics Committee (NBC)	Not attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product. (For Local Manufacturer GMP or Registration letter)	Attached
14	Pre-clinical/clinical safety studies	Provided as in Investigator Brochure.
15	Summary of the Protocol	Attached
16	Summary of the Investigator Brochure	Provided as in Investigator Brochure
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Total of 160 IDA subject (woman patient). 80 subjects for test product and 80 for reference product.

19	Name of Monitors & Clinical Research Associate.	Provided as in Final Protocol.
20	Evidence of registration in country of origin.	Not Attached
21	Evidence of registration in Pakistan.	Attached
22	Sample of label of the investigational product / drug.	Attached
23	Duration of trial	8 months for completion of clinical part of the trial; whereas, estimated one month would be required for analysis of data.

Following deficiencies were identified:

i. The clinical trial sites of Department of obstetrics and Gynaecology, JPMC, Karachi; Sobhraj Maternity Hospital Karachi; and Karachi Medical Complex are not licensed with DRAP neither the hospitals have applied for their license;

ii. The approval from the National Bioethics Committee has not been attached with the application;

iii. The sites are not approved by the IRB/ethics committee; and

iv. Undertaking on stamp paper is not provided and fee is not submitted.

After evaluation observations/shortcoming were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017 and were accordingly communicated to the firm on 23rd January, 2019, response is still awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

6) Application of M/s Pharma Professional for Approval and Registration of Comparative Clinical Study of Injection Megafer.

Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and safety of test product **Megafer Injection ®** manufactured by M/s Surge Laboratories (PVT) Ltd, Karachi, compared with reference product **Venofer Injection ®,** manufactured by M/s (Vifor International) Inc, in woman with Iron deficiency Anaemia (IDA).

2. The short summary of the proposed study is as under;

x. **Study title:** A comparative, open labelled, multicentre, parallel arm, controlled, and randomized study with 2 parallel groups to compare the efficacy and safety of

test drug (Megafer Injection) with reference (Venofer Injection) in outpatient woman with Iron deficiency anaemia (IDA).

xi. **Investigational Product:** Megafer Injection ® (Iron Sucrose) manufactured by M/s Surge Laboratories (PVT) Ltd, Karachi.

xii. Reference Product: Venofer Injection ® (Iron Sucrose), manufactured by M/s (Vifor International) Inc.

xiii. **Sponsor & Manufacturer:** M/s Surge Laboratories (PVT) Ltd, Karachi.

xiv. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.

xv. **Study Sites:**

a. Department of Obstetrics and Gynaecology, JPMC, Karachi; and
b. Sobhraj Maternity Hospital Karachi.

xvi. **Principal Investigator:** Dr. Haleema Yasmin.

xvii. **Funding Source**: The sponsor

xviii. **Cost of the Project**: 3,000,000 PKRs (approximately).

The details of the submitted documents as per checklist are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Application submitted as per Form-II of the Bio study Rules, 2017.
2	Fee	Not provided
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries if applicable	Conduct in Pakistan
7	Phase of trial.	Post-marketing study (Phase-IV)
8	Quantity of drug / trial material to be imported/ procured.	Reference Product: *Total 550 ampoules (400 ampoules for 40 subjects and remaining to be retained as per GCP standards)* Test Product: *Total 550 ampoules (400 ampoules for 40 subjects and remaining to be retained as per GCP standards)*
9	Site (s) of the trial.	i. Department of Obstetrics and Gynaecology, JPMC, Karachi; and ii. Sobhraj Maternity Hospital Karachi.

		Both the sites are not yet licensed by the DRAP neither the firm had applied for it.
10	CVs of the Investigators	Attached
11	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval of trial and composition of the IRB provided; but the approval of the site by the IRB is not attached with application.
12	Approval of National Bio-ethics Committee (NBC)	Not attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product. (For Local Manufacturer GMP or Registration letter)	Attached
14	Pre-clinical/clinical safety studies	Provided as in Investigator Brochure.
15	Summary of the Protocol	Attached
16	Summary of the Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	80 woman subjects with iron deficiency anemia (40 subjects for test and 40 subject for reference product).
19	Name of Monitors & Clinical Research Associate.	Provided as in Investigator Brochure
20	Evidence of registration in country of origin.	Not Attached
21	Evidence of registration in Pakistan.	Attached
22	Sample of label of the investigational product / drug.	Attached
23	Duration of trial	Clinical part of the trail will be completed in 6 months; whereas, for the analysis of date estimated one month would be required.

Following deficiencies were identified:

i. The clinical trial sites of Department of Obstetrics and Gynaecology, JPMC, Karachi and Sobhraj Maternity Hospital Karachi are not licensed with DRAP neither the hospitals have applied for their license;

ii. The approval from the National Bio Ethic committee has not been attached with the application;

iii. The sites are not approved by the IRB/ ethics-committee; and

iv. Undertaking on stamp paper is not provided and fee is not submitted.

After evaluation observations/shortcoming were recorded as per prerequisites of prescribed Form-II of the Bio-Study Rules 2017 and were accordingly communicated to the firm on 23rd January, 2019, response is still awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

7) Application of M/s Pharma Professional for Approval and Registration of Comparative Clinical Study of *Rexyl* ® Cough Syrup.

Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and safety of test product **Rexyl ® cough syrup** manufactured by M/s Nabiqasim Industries (Pvt) Ltd, Karachi, compared with reference product **Hydryllin ® cough syrup,** Manufactured by M/s The Searle Company Ltd in adult outpatients with productive cough.

2. The short summary of the proposed study is as under;

i. **Study title:** An open labelled, controlled, and randomized study with 2 parallel groups to compare the efficacy and safety of test drug (Rexyl cough syrup) with reference (Hydryllin cough syrup) in adult outpatients with productive cough.
ii. **Investigational Product:** Rexyl ® cough syrup (Aminophylline, Ammonium Chloride, Diphenhydramine and menthol), manufactured by Nabiqasim Industries (Pvt) limited, Karachi.
iii. **Reference Product:** Hydryllin ® cough syrup (Aminophylline, Ammonium Chloride, Diphenhydramine and Menthol) manufactured by the Searle Company Ltd.
iv. **Sponsor & Manufacturer:** M/s Nabiqasim Industries (Pvt) Ltd, Karachi.
v. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.
vi. **Study Site:** Karachi Medical Complex, Gulshan-e- Iqbal, Karachi.
vii. **Principal Investigator:** Prof Dr. M. Rafiq Khanani.
viii. **Funding Source**: The sponsor
ix. **Cost of the Project**: 20,000,00 PKRs (approximately)

The details of the submitted documents as per checklist are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Application submitted as per Form-II of the Bio study Rules, 2017.
2	Fee	Not provided
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached

5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries if applicable	Conduct in Pakistan.
7	Phase of trial.	Post-marketing study (Phase-IV)
8	Quantity of drug / trial material to be imported/ procured.	Reference Product: *Total 600 Bottles (300 for 100 subjects and 300 would be retained as per GCP standards).* Test Product: Total 600 bottles (*300 for 100 subjects and 300 would be retained as per GCP standards).*
9	Site (s) of the trial.	Karachi Medical Complex, Karachi (Not approved by the CSC)
10	CVs of the Investigators	Attached
11	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval of trial and composition of the IRB provided; but the approval of the site by the IRB is not attached with application.
12	Approval of National Bio-ethics Committee (NBC)	Not attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product. (For Local Manufacturer GMP or Registration letter)	Attached
14	Pre-clinical/clinical safety studies	Provided as in Investigator Brochure.
15	Summary of the Protocol	Attached
16	Summary of the Investigator Brochure	Provided as in Investigator Brochure.
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Total of 200 subject (100 subjects for test and 100 subjects for reference drug)
19	Name of Monitors & Clinical Research Associate.	Provided as in Investigator Brochure
20	Evidence of registration in country of origin.	NA
21	Evidence of registration in Pakistan.	Attached
22	Sample of label of the investigational product / drug	Attached
23	Duration of trial	Clinical part will be completed in 6 months; whereas, 1 month would be required for analysis of data.

Following deficiencies were identified:

i. The clinical trial site of Karachi Medical Complex is not licensed with DRAP neither the hospital had applied for its license;
ii. The approval from the National Bio Ethic committee has not been attached with the application;
iii. The clinical site is not approved by the IRB (ethics-committee); and
iv. Undertaking on stamp paper is not provided and fee is not submitted.

After evaluation observations/shortcoming were recorded as per prerequisites of prescribed **Form-II** of the **Bio-Study Rules 2017 and were accordingly communicated to the firm on 23rd January, 2019,** response is still awaited**.**

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

8) An International, Multi-Centre Controlled Randomized Clinical Trial to Evaluate Rifampicin 1200 Mg and 1800 Mg Daily in the Reduction of Treatment Duration for Pulmonary Tuberculosis from 06 Months to 04 Months.

Application is from Dr. Bushra Jamil, Agha Khan University, Karachi, wherein the request has been made for approval of clinical trial, which will be carried out at Agha Khan University Hospital, Karachi and Shaukat Khanum Memorial Cancer Hospital, Lahore.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

The details of the submitted documents as per checklist are as under;

S. No.	Required Documents	Remarks
1.	Application along with Fee	Application on Form – II is submitted along with original copy of bank receipt of deposited fee
2.	Investigator Brochure	Attached
3.	Final Protocol	Protocol Version 6.0 dated 15th June, 2017, has been provided.
4.	Informed consent form (English & Urdu)	Attached

5.	List of participating countries (If applicable)	07 countries including Botswana, Peru, Uganda, Nepal, Mexico, Republic of Guinea and Pakistan.
6.	Phase of trial	Phase – III
7.	Quantity of Drug(s) to be imported/procured/manufactured for the trial	Attached
8.	Site(s) of the trial	Trial will be conducted at following two sites in Pakistan; 1. The Aga Khan University Hospital, Karachi. 2. Shaukat Khanum Memorial Cancer Hospital, Lahore.
9.	C.Vs of investigator(s)	CVs of both Investigators are attached.
10.	Ethical committee approval with complete composition of committee i.e Name and designations of the members	Attached
11.	Approval from National Bio-ethics Committee (PHRC)	NBC Approval vide letter No.4-87/NBC-329/18/337, dated 10th August, 2018, is attached.
12.	GMP certificate along with Free Sale Certificate/Certificate of Pharmaceutical Product (Note: For locally manufactured product GMP Cert., COA of the Product and Registration Letter will be required)	GMP Certificates of M/s Macleods Pharmaceuticals Limited, India and M/s SW Pharma GmbH, Germany have been provided. However, no CoPP or Free Sale Certificates of the investigational products, have been furnished.
13.	Pre-clinical, clinical data and safety studies.	Attached
14.	Summary of the protocol	Attached
15.	Summary of the Investigator Brochure	Not provided
16.	Adverse Event Reporting form	Attached
17.	No. of Patients to be enrolled in each center	It is mentioned that a total of 100 patients will be enrolled in Pakistan.
18.	Name of monitors/clinical research associate	Attached
19.	Evidence of registration of study drug in country of origin	Not provided.

20.	Copy of registration letter (if drug is registered in Pakistan)	The investigational material will be imported from India and Germany
21.	Sample of label of drug	Attached
22.	Duration of trial	24 Months

Following deficiencies were identified:

i) The evidence of registration/marketing authorization of all investigational products in the country of origin along with their CoPPs and Free Sale Certificates.

ii) Authorization of the sponsor to conduct the subject trial in Pakistan.

iii) The proposed clinical trial sites i.e. Aga Khan University Hospital, Karachi and Shaukat Khanum Memorial Cancer Hospital, Lahore, are required to be licensed as Clinical Trial Sites, under the Bio-study Rules, 2017.

iv) Apart from the proposed clinical trial site, the role of Aga Khan University, Karachi, in the subject clinical trial, is not well defined.

v) The mechanism for monitoring and oversight of the subject clinical trial in Pakistan and responsible person/firm for the said purpose, needs to be defined.

The firm was communicated of the above shortcomings through letter no. F.No.3-6/2018 DD (PS), dated 12th December, 2018, But still response is awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their clinical study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

AGENDA ITEM NO. IV: BA/BE Studies Registration

Discussion Agenda Item No IV: The Committee was informed that all the cases for registration of BA/BE studies under agenda item No. IV were incomplete. The applicants required licensing of their BA/BE Centre and submission of fee (approved and notified by DRAP) was pending.

The applications submitted for registration of BA/BE Studies as per **Form-IIA** under the **Bio-Study Rules 2017** as follows:

1) Bioequivalence Study of Lamnet (Lamotrigine BP) 100mg Tablet of M/s Searle Company Ltd, at Center for Bioequivalence Study and Clinical Research (CBSCR), (ICCBS), F. No. 14-6/2018 DD (PS).

Application is from General Manage Dr. Raza Shah, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017 dated 19-01-2018.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence Lamnet (Lamotrigine) 100mg Tablet with reference product Lamictal (Lamotrigine) 100mg Tablet under the fasting conditions in Healthy Male Pakistani Subjects.
ii. **Investigational Product:** Lamnet (Lamotrigine) 100mg Tablet of M/s Searle Company Ltd.
iii. **Reference Product:** Lamictal (Lamotrigine) 100mg Tablet of M/s GlaxoSmithKline Pakistan, Limited
iv. **Sponsor & Manufacturer:** M/s the Searle Company Limited, Karachi.
v. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.
vi. **Principal Investigator:** Dr. Muhammad Raza Shah
vii. **Co-Principal Investigator:** Dr. Naghma Hashmi
viii. **Funding Source**: The sponsor
ix. **Cost of the Project**: Rs.20,00,000 (approximately)

The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	50000 Processing fee for the study has been deposited.
3	Formulation of Investigational Product	Attached
4	Purpose of Study along with its cost and source of fund	Attached
5	Proposed center for study	CBSCR, ICCBS Not yet approved by the DRAP.
6	Investigational Design and Study Plan	Attached
7	Pre-clinical or clinical data or safety studies	Not applicable.
8	Final protocol	Attached
9	Detail of Investigators	Attached

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	The applicant has informed that the IRB approval is still under process.
11	Approval of National Bio-ethics Committee (NBC)	Provided
12	Informed consent and participant information sheet (Urdu to English)	Attached
13	Summary of Protocol and Investigator Brochure	Attached
14	Adverse Event Reporting Form	Attached
15	Name of Monitors & Clinical Research Associate	Attached
16	Proof of Registration of Investigational Product in Pakistan	Attached
17	Quantity of Investigational Product	Reference Product: 80 Tablets Test Product: 110 Tablets

Description of shortcomings:

Following deficiencies were identified:

i) BA/BE Centre of CBSCR), ICCBS is not yet licensed by the DRAP.

ii) Applicant is already advised to apply separately for the license of each facility of BA/BE Studies Center, Clinical Trial Site and CRO on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) The approval of Institutional Review Board (IRB) has not yet been provided.

iv) Undertaking on stamp paper is not provided.

The firm was communicated through letter on 09th October, 2018, after scrutiny of the reply another letter sent on 11th January, 2019, to apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for approval of BA/BE Studies under the Bio-Study Rule 2017, the firm accordingly submitted the Bio-ethics approval, only.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their BA/BE study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

2) Bioequivalence Study of Moksi (Moxifloxacin) 400mg Tablet, of M/s Searle Company Ltd, at Center for Bioequivalence Study and Clinical Research (CBSCR), (ICCBS), F. No. 14-3/2018 DD (PS)

Application is from General Manager, Dr. M. Raza Shah, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Relative Bioavailability of **Moksi (Moxifloxacin) 400mg Tablet** of M/s Abbott Laboratories and **Avelox (Moxifloxacin) 400mg Tablet** of M/s Bayer Pharmaceuticals under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Moksi (Moxifloxacin) 400mg Tablet

iii. **Reference Product:** Avelox (Moxifloxacin) 400mg Tablet of M/s Bayer Pharma

iv. **Sponsor & Manufacturer:** M/s Abbott Laboratories (Pakistan) Ltd., Karachi.

v. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

viii. **Funding Source**: The sponsor

ix. **Cost of the Project**: Rs.3800,000 (approximately)

3. The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	Processing fee of Rs.50000 for the study has been deposited.
3	Formulation of Investigational Product	Attached
4	Purpose of Study along with its cost and source of fund	Attached
5	Proposed center for study	CBSCR, ICCBS Not yet approved
6	Investigational Design and Study Plan	Attached

7	Pre-clinical or clinical data or safety studies	Not applicable
8	Final protocol	Attached
9	Detail of Investigators	Attached
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	The applicant has informed that the IRB approval is still under process.
11	Approval of National Bio-ethics Committee (NBC)	Not attached.
12	Informed consent and participant information sheet (Urdu to English)	Attached
13	Summary of Protocol and Investigator Brochure	Attached
14	Adverse Event Reporting Form	Attached
15	Name of Monitors & Clinical Research Associate	Attached
16	Proof of Registration of Investigational Product in Pakistan	Attached
17	Quantity of Investigational Product	Reference Product: 350 Tablets Test Product: 350 Tablets

Description of shortcomings:

Following deficiencies were identified:

i) BA/BE centre of CBSCR, ICCBS is not yet licensed by the DRAP.

ii) Applicant is already advised to apply separately for the license of each facility of BA/BE Studies Center, Clinical Trial Site and CRO on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) The approval of Institutional Review Board (IRB) and NBC has not yet been provided yet.

iv) Undertaking on stamp paper is not provided.

The firm was communicated through letter on 09th October, 2018, after scrutiny of the reply another letter sent on 11th January, 2019, to apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for the approval of BA/BE Studies under the Bio-Study Rule 2017, but still response is awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their BA/BE study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

3) Bioequivalence Study of Xorban (Rivaroxaban) 20mg Tablet, of M/s Searle Company Ltd, at Center for Bioequivalence Study and Clinical Research (CBSCR), (ICCBS), F. No. 14-4/2018 DD (PS)

Application is from General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence of Xaroban 20mg (Rivaroxaban) tablet Manufactured by The Searle Company Limited, with reference product Xarelto 20mg (Rivaroxaban) Tablet manufactured by Bayer Healthcare Pharmaceuticals under Fed conditions in Healthy male Pakistani Subjects.

ii. **Investigational Product:** Xaroban 20mg (Rivaroxaban) tablet Manufactured by The Searle Company Limited

iii. **Reference Product:** Xarelto 20mg (Rivaroxaban) Tablet manufactured by Bayer Healthcare Pharmaceuticals

iv. **Sponsor & Manufacturer:** M/s the Searle Company Limited, Karachi.

v. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

viii. **Funding Source**: The sponsor

ix. **Cost of the Project**: Rs.22,00,000 (approximately)

3. The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	Processing fee of Rs.50000 for the study has been deposited.
3	Formulation of Investigational Product	Attached
4	Purpose of Study along with its cost and source of fund	Attached
5	Proposed center for study	CBSCR, ICCBS Not approved yet
6	Investigational Design and Study Plan	Attached

7	Pre-clinical or clinical data or safety studies	Not applicable
8	Final protocol	Attached
9	Detail of Investigators	Attached
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	The applicant has informed that the IRB approval is still under process.
11	Approval of National Bio-ethics Committee (NBC)	Attached.
12	Informed consent and participant information sheet (Urdu to English)	Attached
13	Summary of Protocol and Investigator Brochure	Attached
14	Adverse Event Reporting Form	Attached
15	Name of Monitors & Clinical Research Associate	Attached
16	Proof of Registration of Investigational Product in Pakistan	Attached
17	Quantity of Investigational Product	Reference Product: 110 Tablets Test Product: 110 Tablets

Description of shortcomings:

Following deficiencies were identified:

i) BA/BE centre of CBSCR, ICCBS is not yet licensed by the DRAP.

ii) Applicant is already advised to apply separately for the license of each facility of BA/BE Studies Center, Clinical Trial Site and CRO on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) Undertaking on stamp paper is not provided.

iv) The approval of Institutional Review Board (IRB) has not yet been provided.

The firm was communicated through letter on 09th October, 2018, after scrutiny of the reply another letter sent on 11th January, 2019, to apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for the approval of BA/BE Studies under the Bio-Study Rule 2017. The firm, accordingly, submitted Bio-ethics committee approval, only.

Decision: The CSC decided to call the applicant along with the Principal Investigator to appear before the Committee, in its next meeting and give a 7 to 8 minutes presentation on their BA/BE study. In the meantime, the applicant be conveyed to fulfill the shortcomings and submit fee as approved by the Authority.

4) <u>Bioequivalence Study of Vaptor (Rosuvastatin) 20mg Tablet, of M/s Searle Company Ltd, at Center for Bioequivalence Study and Clinical Research (CBSCR), (ICCBS), F. No. 14-5/2018 DD (PS)</u>

Application is from General Manager Dr. M.Raza Shah, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

x. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence Vaptor (Rosuvastatin) 20mg Tablet manufactured by the Searle Company Pakistan Limited with reference product Crestor 20mg (Rosuvastatin) Tablet manufactured by AstraZeneca Pharmaceuticals under the fasting conditions in Healthy Male Pakistani Subjects.

xi. **Investigational Product:** Vaptor (Rosuvastatin) 20mg Tablet of M/s Searle Company Ltd.

xii. **Reference Product:** Crestor (Rosuvastatin) 20mg Tablet of M/s AstraZeneca Pharmaceuticals

xiii. **Sponsor & Manufacturer:** M/s the Searle Company Limited, Karachi.

xiv. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

xv. **Principal Investigator:** Dr. Muhammad Raza Shah

xvi. **Co-Principal Investigator:** Dr. Naghma Hashmi

xvii. **Funding Source**: The sponsor

xviii. **Cost of the Project**: Rs.30,00,000 (approximately)

3. The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	Processing fee of Rs.50000 for the study has been deposited.
3	Formulation of Investigational Product	Attached
4	Purpose of Study along with its cost and source of fund	Attached
5	Proposed center for study	CBSCR, ICCBS

		Not approved yet
6	Investigational Design and Study Plan	Attached
7	Pre-clinical or clinical data or safety studies	Not applicable.
8	Final protocol	Attached
9	Detail of Investigators	Attached
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	The applicant has informed that the IRB approval is still under process.
11	Approval of National Bio-ethics Committee (NBC)	Provided
12	Informed consent and participant information sheet (Urdu to English)	Attached
13	Summary of Protocol and Investigator Brochure	Attached
14	Adverse Event Reporting Form	Attached
15	Name of Monitors & Clinical Research Associate	Attached
16	Proof of Registration of Investigational Product in Pakistan	Attached
17	Quantity of Investigational Product	Reference Product: 80 Tablets Test Product: 80 Tablets

Description of shortcomings:

Following deficiencies were identified:

i) BA/BE centre of CBSCR, ICCBS is not yet licensed by the DRAP.

ii) Applicant is already advised to apply separately for the license of each facility of BA/BE Studies Center, Clinical Trial Site and CRO on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) Undertaking on stamp paper is not provided.

iv) The approval of Institutional Review Board (IRB) has not yet been provided

The firm was communicated through letter on 09th October, 2018, after scrutiny of the reply another letter sent on 11th January, 2019 to apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for approval of BA/BE Studies under the Bio-Study Rule 2017. The firm accordingly, submitted the approval of Bio-ethics committee, only.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their BA/BE study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

5) <u>Bioequivalence Study of Dextop (Dexlansoprazole) 60mg Tablet, of M/s Searle Company Ltd, at Center for Bioequivalence Study and Clinical Research (CBSCR), (ICCBS), F. No. 15-1/2018 DD (PS)</u>

Application is from General Manager, Dr. M. Raza Shah, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, One Period Study to explore the Pharmacokinetics of Dextop (Dexlansoprazole) 60mg Capsules under the fasting conditions in Healthy Male Pakistani Subjects.
ii. **Investigational Product:** Dextop (Dexlansoprazole) 60mg Capsules of M/s Searle Company Ltd.
iii. **Sponsor & Manufacturer:** M/s The Searle Company Limited, Karachi.
iv. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.
v. **Principal Investigator:** Dr. Muhammad Raza Shah
vi. **Co-Principal Investigator:** Dr. Naghma Hashmi
vii. **Funding Source**: The sponsor
viii. **Cost of the Project**: Rs.15,00,000 (approximately)

3. The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	Processing fee of Rs.50000 for the study has been deposited.
3	Formulation of Investigational Product	Attached
4	Purpose of Study along with its cost and source of fund	Attached
5	Proposed center for study	CBSCR, ICCBS Not approved yet
6	Investigational Design and Study Plan	Attached
7	Pre-clinical or clinical data or safety studies	Not applicable.
8	Final protocol	Attached
9	Detail of Investigators	Attached

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	The applicant has informed that the IRB approval is still under process.
11	Approval of National Bio-ethics Committee (NBC)	Provided
12	Informed consent and participant information sheet (Urdu to English)	Attached
13	Summary of Protocol and Investigator Brochure	Attached
14	Adverse Event Reporting Form	Attached
15	Name of Monitors & Clinical Research Associate	Attached
16	Proof of Registration of Investigational Product in Pakistan	Attached
17	Quantity of Investigational Product	100 Capsules

Description of shortcomings

Following deficiencies were identified:

i) BA/BE centre of CBSCR, ICCBS is not yet licensed by the DRAP.

ii) Applicant is already advised to apply separately for the license of each facility of BA/BE Studies Center, Clinical Trial Site and CRO on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) Undertaking on stamp paper is not provided.

iv) The approval of Institutional Review Board (IRB) has not yet been provided.

The firm was communicated through on 09th October, 2018 to apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for the approval of BA/BE Studies under the Bio-Study Rule 2017. The firm accordingly, submitted the approval of Bio-ethic committee only.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their BA/BE study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

6) Bioequivalence Study of *Clarithro*® (Clarithromycin) 500mg Tablet, of M/s Nabiqasim Industries Ltd, at Pharma Professional Services, F. No. 14-7/2018 DD (PS)

Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

After evaluation following observations were recorded as per prerequisites of prescribed **Form-IIA** of the **Bio-Study Rules 2017.**

The short summary of the proposed study is as under;

i. **Study title:** An open labelled Two period, Two Treatments, Two Sequences, Single Dose, Single Dose, Randomized, Crossover Bioequivalence Study Of Clarithromycin (Clarithro) 500mg Tablets in Healthy Volunteers, Compared to equivalent drug dose in reference formulation of KLARICID 500mg Tablets under fasting condition.

ii. **Investigational Product:** Clarithro® (Clarithromycin) 500mg Tablets of M/s Nabi Qasim (Pvt) Ltd and Klaricid® (Clarithromycin) 500mg Tablets of M/s Abbott Laboratories, Karachi

iii. **Sponsor & Manufacturer:** M/s Nabiqasim Industries (Pvt) Ltd, Karachi.

iv. **CRO and Study Site:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.

v. **Principal Investigator:** Prof. Dr. Tasneem Ahmad

vi. **Funding Source**: The sponsor

vii. **Cost of the Project**: Rs.3,000,000 (approximately)

3. The details of the submitted documents as per checklist are as under;

S. No.	Document	Remarks
1	Application	Application has been submitted on prescribed Form – IIA, under the Bio-study Rules, 2017
2	Fee	Not Provided
3	Formulation of Investigational Product	Attached
4	Pharmacodynamics and Pharmacokinetics of Investigational Product	Attached
5	Purpose of Study along with its cost and source of fund	Study Objective: To determine the Bioequivalence of Test Product Clarithro® 500mg Tablets, manufactured by M/s Nabiqasim Industries (Pvt) Ltd, Karachi, Pakistan, in healthy Adult Human Subjects, compared with Reference Product: Klaricid® 500mg Tablet, manufactured by Abbott Laboratories, Karachi, Pakistan. Study Purpose: To evaluate the bioequivalence of test product (Clarithro®) as a generic replacement for the reference product (Klaricid®) Anticipated Cost of Project PKR 3,000,000/-

6	Proposed center for study	M/s Pharma Professional Services (Pvt) Ltd, Karachi.
7	Investigational Design and Study Plan	To investigate average bioequivalence in a 2x2 Crossover design in humans. Attached
8	Investigational design and study plan	Attached
9	Pre-clinical or clinical data or safety studies	Attached
10	Final protocol	Attached
11	Detail of the investigator (Principal investigator, analysts and others along with CV)	Attached
12	IRB approval	Attached
13	Ethical committee composition (names and designations)	Attached
14	Site approval by the Ethics committee	Attached
15	Informed consent (English and Urdu)	Attached
16	Summary of the protocol or synopsis (Investigational Product)	100 Capsules
17	Adverse Event Reporting Form	Attached
18	Name of the monitor or clinical research associate	Attached
19	Evidence of registration in country of origin (GMP certificate along with CoPP or Free sale certificate)	Attached
20	Copy of registration letter if registered in Pakistan	Attached
21	Proposed label of investigational product	Attached
22	Quantity of investigational product to be used in the study along with justification (Note: All the quantities of the each of investigational product should be procured from one single source)	Reference Product: 120 Tablets Test Product: 120 Tablets

Description of shortcomings:

Following deficiencies were identified:

i) It is mandatory to get approval of the BA/BE Studies Center before approval or registration of BA/BE Studies, but the applied center is still not approved/ licensed with DRAP.

ii) Applicant advised to apply for BA/BE Studies Center approval on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) Applicant advised to submit prescribed fee for processing of application apply for BA/BE Studies Center approval on prescribed Form-I of the Bio-Studies Rules along with prerequisites.

iii) The approval of Institutional Review Board (IRB) of medical teaching institutions and National Bioethics Committee (NBC) of Pakistan, is prerequisite to conduct above mentioned studies under the Bio Study Rules, 2017.

The firm was communicated through letter no. F.No.14-7/2018 DD (PS), dated 09th October, 2018, that apply on prescribed Form-I for BA/BE Studies site approval and fulfill all prerequisites for approval of BA/BE Studies approval under the Bio-Study Rule 2017, But still response is awaited.

Decision: The CSC decided to call the applicant/Principal Investigator to give a 7 to 8 minutes presentation on their BA/BE study before the CSC in the next meeting. The committee also decided, that the applicant be conveyed to fulfill the shortcomings for completion of application and submit fee which has been approved by the Authority.

Agenda Item No. V: Closure of Trial on Completion

1) Regulatory Submission for Multi-Country Clinical Trial "A Phase II Study to Evaluate the safety, tolerability and Pharmacodynamics of Pegylated Interferon Lambda Monotherapy in Patients with Chronic Hepatitis Delta Virus Infection".

Discussion of CSC: Dr. Javed Akram pointed out that before closure of a trial on completion an inspection of trial site after completion must be conducted for its final monitoring/evaluation report.

The Case detail is as under:

262nd Meeting of Registration Board:

The case was placed before the Drug Registration Board in its 262nd Meeting held on 20th October, 2016. In the light of discussion and deliberations, the Board granted the approvals for following points;

i) ***Clinical trial namely "A Phase II Study to Evaluate the Safety. Tolerability and Pharmacodynamics of Pegylated Interferon Lambda Mono-therapy in Patients with Chronic Hepatitis Delta Virus (HDV) Infection".***

ii) ***Proposed trial site i.e. Medicine Department, Aga Khan University Hospital, Karachi.***

iii) ***Principal Investigator namely Prof. Dr. Saeed Sadiq Hamid, Consultant Gastroenterologist, Department of Medicine, Aga Khan University Hospital, Karachi.***

iv) ***To import the proportionate trial material as per requirement of the study/protocol in compliance to provisions of the Drugs (Import & Export) Rules, 1976."***

v) ***Secondary objectives also include to evaluate the effect of treatment with two dose levels of Lambda on Gamma – glutamyl Trans peptidase (GGT)***

In the light of above decision of Drug Registration Board, **approval letter** was issued. The applicant submitted amendments in the study protocol and provided the supporting documents.

Request to import more Investigational Product:

The applicant submitted for approval to import 600 more syringes of the investigational product (PEG Interferon Lambda 120 µg / 180µg). It has been stated that out of their already approved quantity of 750 syringes, 200 syringes have been destroyed due to temperature excursion at airport storage and target enrollment has been increased to forty patients (20 in each group).

Scrutiny of Record:

During the evaluation of the record provided by the applicants regarding the destruction of 200 syringes following discrepancies were found:

(i) It was claimed that 87 PFS of the investigational product were destroyed due to expiry but the Expiry Date of the same batch (B. No.3K77275) is mentioned in the different inventory sheets as June, 2018 and June, 2017 which is questionable.

(ii) The destroyed quantities of 200 prefilled syringes due to temperature excursion, included 100 each of both strengths (120µg and 180µg) whereas the import documents reveal that all the 200 syringes were of 180µg. technically, two different potencies of the product cannot have the same batch number.

(iii) The CRO/P.I did not furnished the required documents especially the invoices of the shipments of the investigational product, imported and got cleared from the DRAP, Karachi office.

Point of View of Applicant:

The applicant in their later letter informed that they were unaware of the law and due to which they could not inform the authority about destruction of the investigational material and further they ensured that this practice will not be repeated again. They further informed that they wanted to import 600 injections of Lambda Interferon 180µg only and if a patient is randomized for 120µg treatment group then they will instruct the patient to administer 120µg from the same syringe and remaining 60µg will be destroyed.

Scrutiny of Record:

The applicant did not furnish the copies of the invoices of imported investigational material.

The applicant did not clearly explain that how 120µg will be administered from 180µg syringe. It is also not clear that which potency of the investigational product was previously imported. The justification for further import of 600 PFS of Lambda Interferon 180µg was not been provided by the applicant.

Request of Principal Investigator:

The principal investigator Dr. Saeed Hamid informed that destruction of 200 syringes of the study drug resulted in its shortage and now there is possibility that the recruited patients may withdraw from the study due to non-availability of medication.

The applicant requested to grant **provisional approval to import additional quantity of 200 syringes** of the investigational product so that the patients can continue their treatment.

It has been further stated that only 180µg potency of the study drug is being manufactured and imported. For patients randomized to 120µg treatment group, the syringe is adjusted to 120µg by discarding the extra drug up to the defined mark on the syringe, before use which is not in line with the approved protocol. Hence if this practice is to be followed then permission of the Registration Board will be required.

The applicant justified the quantity of 600 syringes for further import by calculating that so far they have enrolled 15 patients and each patient is being provided with 05 syringes every month, which includes four syringes for weekly dose and one extra syringe to cover any wastage or loss of the study drug. In this way, they require 75 syringes every month and for remaining eighth months of treatment period from October, 2017 to May 2018, they will require a total of 600 syringes.

275th Meeting of Registration Board:

The case was presented before the Drug Registration Board in its 275th meeting dated 25th and 26th October, 2017.

The decision of the Board is reproduced as under:

After hearing the opinion of the representative of the trial management and in the light of discussion and deliberation, the Board decided the matter as under;

i) The Registration Board approved the submitted revised Protocol (Amendment 3) and allowed the Trial Management to import the requested quantity of 600 Pre-filled Syringes of Pegylated Interferon Lambda 180µg, on immediate basis.

ii) The Board directed the Pharmacy Services Division for strict monitoring of the Trial and utilization of the Investigational Drug, on regular basis, till the completion of the trial.

iii) The Board also directed the Pharmacy Services Division to communicate the above decision, immediately to the applicant, without waiting for the approval of the minutes of the meeting.

Case Before CSC: (Closure of Trial after Completion and Permission to destroy unused Investigational Product):

The Committee was briefed that the Principal Investigator, Dr. Saeed Hamid, Agha Khan University, Karachi, requested for "approval to incinerate remaining unused investigational product", received on 24.12.2018. The applicant informed that the trial "LIMT-1 Trial: A phase 2 study to evaluate the safety, tolerability, and pharmacodynamics of Pegylated Interferon Lambda Monotherapy in Patients with Chronic Hepatitis Delta Virus Infection" has been completed and they want its closure phase and as per sponsors recommendations they want to incinerate the remaining expired, unused investigational products i.e. 180 mcg prefilled Pegylated interferon lambda-1 a syringes. The committee was also informed that the report after completion has not been submitted by the applicant.

Decision Agenda Item No V: The committee decided to include the case for inspection of trial site after formulation of inspection pool and in the meantime the applicant be conveyed to submit final report on completion of trial as required under the Bio-study Rules 2017.

Agenda Item VI: Miscellaneous Recommendations of CSC:

The committee recommended that, prior to placing a clinical research or BE/BA study as agenda before the Clinical Studies Committee for grant of registration, reviews from expert may be sought, for this purpose a National Review Board may be formed who can effectively go through all the aspects of the study beforehand and submit comments/report to CSC with the case for consideration. The National Review Board be formed and notified by the Chairman CSC, CEO (DRAP) and Prof. Dr. Javed Akram (VC, UHS).

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