Regulatory Guidelines for Centers performing Bioavailability and Bioequivalence Studies

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1. Introduction:

Identifying all of the main points required to organize the workflow and conduct the bioavailability and bioequivalence studies in the centers licensed by Egyptian Drug Authority conducting the bioavailability and bioequivalence studies in accordance with the decision of the Bioavailability and Bioequivalence Studies Evaluation Committee issued on: 18th, June 2022.

2. Scope of implementation

The centers that conduct bioavailability, bioequivalence and Comparative in-vitro studies licensed by Egyptian Drug Authority.

3. Definitions:

Bioavailability:

Bioavailability can be defined as the rate and extent to which the active pharmaceutical ingredient or active moisture is absorbed from a pharmaceutical dosage form and becomes available in the general circulation.

Bioequivalence:

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and area under the curve (AUC) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Biowaiver:

The term biowaiver is applied to a regulatory drug approval process based on evidence of equivalence other than through in vivo equivalence testing.

4. Procedures

First: The organizing rules of conducting bioavailability, bioequivalence and Comparative in-vitro studies in the centers:

1. A sample withdraw report for bioavailability or bioequivalence studies or Comparative in-vitro studies shall be provided. The report must indicate the name of the bioavailability and bioequivalence center, provided that it must be issued by the inspector of the General Administration of Factories Inspection in the Central Administration of Operations in Egyptian Drug Authority.
2. The center must have a sufficient quantity of (Test & Reference Products) to conduct the study (bioavailability study, bioequivalence study or Comparative in-vitro studies in the centers).
3. In case of conducting the bioequivalence studies for (Modified Release Products), the study must be conducted in (Fasting & Fed States), except for bioequivalence studies for (Delayed release or Enteric Coated Products), in the study should be conducted in the fasting state only. provided that in case of conducting two bioequivalence studies as follows: "Two Separate Two-Way Cross-Over" the two bioequivalence studies in the fasting and fed states shall be sent in the form of two separate files and the part of "Bioanalytical Method and validation & Invitro Part" only once in one of the two files.
4. With regard to conducting Comparative in-vitro studies in the centers (As a Biowaiver or a Complementary for In - vivo studies)

The study must be conducted as follows:

- At three different pHs (1.2, 4.5 & 6.8) in addition to the most suitable medium, provided that the most suitable medium shall be chosen according to the method indicated on the website of the American Food and Drug Administration (FDA) or the United States Pharmacopeia (USP)… etc. except for the studies conducted on the (Delayed Release or Enteric Coated Products), where the study shall only conducted according to the reference method stipulated on the website of (FDA) or (USP)… etc. In case of lack to the most suitable medium, **the study shall be conducted as follows**:

- At two pHs (at acidic stage & buffer stage).

5. The Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of Bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of the date in which the Bioavailability or bioequivalence studies are conducted as follows:

- The Center shall notify the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of Availability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the date of conducting each study separately and before a sufficient time; not less than three working days (from Sunday to Thursday from 8 am to 3 pm) and not more than two weeks before the study initiating, via the department's e-mail address:

Hdr.bioequivalence@edaegypt.gov.eg

Taking into account that the center must commit to the following:

1. Submitting the following data of the bioavailability or bioequivalence study:

- Test Product Name & Dosage Form:
- Active Ingredients(s):
- Manufacturer & License Holder:
- Dates of Study Phases: --/--/----
- Study Status: New Study or Repeated Study.
- Study Type: Fasting or Fed Study.
- Study Design.

2. Submitting the following documents of the product for which the bioavailability or bioequivalence study will be conducted:

A- In case of conducting studies on registered pharmaceutical products (on a production batch or a pilot batch according to the withdrawal report issued by the General Administration of Factory Inspection at the Central Administration of Operations in Egyptian Drug Authority), a copy of the latest registration notification of the product under study shall be sent accompanied by a copy of the composition form approved by Egyptian Drug Authority, provided that the registration notification shall be valid and indicating the decision of the

Bioavailability and Bioequivalence Studies Evaluation Committee regarding the type of study required for the product. In case of the company and/or center have submitted a petition to adjudicated on the position of the product in terms of the required study or any matter related to the method of conducting the study and the petition has been presented to the Bioavailability and Bioequivalence Studies Evaluation Committee, a copy of the Committee decision ~~of the said~~ regarding this petition shall be sent.

B- <u>In case of conducting studies on pharmaceutical products under registration</u> (on a pilot batch according to the withdrawal report issued by the General Administration of Factory Inspection at the Central Administration of Operations in Egyptian Drug Authority), a copy of the approval of the Specialized Scientific Committee for Evaluating Stability Studies shall be sent by the company. That copy shall be accompanied by a copy of the composition form approved by the Specialized Scientific Committee for Evaluating Stability Studies. In the case of submitting products for registration under the system (425) of 2015, a copy of the composition form signed by the inspector of the General Administration of Factory Inspection at the Central Administration of Operations in Egyptian Drug Authority shall be sent in addition to a copy of the decision of the Bioavailability and Bioequivalence Studies Evaluation Committee regarding the type of study required for the product under study submitted by the company owning the product. In case of the company and/or center have submitted a petition to adjudicate on the position of the product in terms of any matter relating to the method of conducting the study and the petition has been presented to the Bioavailability and Bioequivalence Studies Evaluation Committee, a copy of the decision of the said Committee regarding this petition shall be sent.

C- <u>In both aforementioned cases (A, B)</u>, a copy of the samples withdraw report of the studies of bioequivalence of the products under study, issued by the General Administration of Factory Inspection at the Central Administration of Operations in Egyptian Drug Authority, shall also be sent, provided that report copy shall indicate the following: (the trade name, concentration and pharmaceutical form of the product, manufacturer name, type of batch (initial production batch, production batch, pilot batch) batch number, manufacturing date and expiration date, type of the required study, name of the bioavailability and equivalence center that will conduct the study, taking into account that the report shall state that the samples were withdrawn after changing the excipient materials or adding a source of the raw material, provided that the new source shall be indicated... "if any").

3. the names list of the names of volunteers participating in the study in the form of a Word Document or Excel Sheet, shall be sent as follows:

SN	The quadruple volunteer's name in Arabic	The volunteer's ID No. consisting of "14 numbers"
1.		

All of the volunteers data must be correct and on the responsibility of the center and a copy of the volunteers' ID No. shall be attached, noting that only forty volunteers are approved by the Department of Protocols Evaluation and Following-up of the Centers of Bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority to participate in the study. The names of the remaining volunteers will not be considered after approving the maximum limit except for some cases that require involving a larger number of the volunteers. The center is allowed to complete the list of volunteer names until the maximum limit is reached within one working day before initiating the study conduct.

4. The Center shall be committed to provide a list of the volunteers names actually participating in the study, the "Attendance Sheet for Volunteers", after each phase of the study. The list shall be submitted in the form of a Word Document or Excel Sheet also as a scanned document after signing it by the volunteers and center officials, **as follows**:

SN	The quadruple volunteer's name in Arabic	The volunteer's ID No. consisting of "14 numbers"
1.		

5. The volunteers participating in the study shall be among the volunteers who have previously been approved by the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority. Any volunteer is not allowed to participate in Bioavailability studies or bioequivalence studies except after obtaining an approval by the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority.

6. The period between the participation of the same volunteer in two consecutive bioequivalence studies is two months starting from the date of the last (Phase) of the previous study.

7. Every volunteer shall have an ID card during the attendance period inside the center. Any volunteer has no ID card is not permitted to participate in bioavailability or bioequivalence studies.

8. The volunteers shall be selected in accordance with Selection Criteria mentioned in the Egyptian rules regulating the conduct of bioavailability and bioequivalence studies.

(6) In case of conducting a bioavailability or bioequivalence study on more than one stage, the following shall be adhered to:

A. The study shall be conducted on no more than two stages.

B. The stages of study shall be indicated in the study protocol.

C. When conducting the study on two stages (Stage I & Stage II), the washout period between the two stages must not exceed two weeks, provided that the washout period between the study (Phases) shall be fixed.

D. The results of the (Stage I) must not significantly statistically different from the results of the (Stage II).

E. The center shall notify the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the date of conducting each (stage) in sufficient time; not less than three working days and not more than two weeks before initiating the relevant stage of the study.

(7) In the case of occurring sudden changes (postponement or cancellation of the bioavailability or bioequivalence study), the following must be adhered to:

A. The Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence & Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of postponement or cancellation of the study no later than the morning of the study day, via the e-mail of the Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products or by telephone in case of necessity.

B. When setting a new date for the study, the center shall notify the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the new study date in sufficient time; not less than three working days and not more than two weeks before initiating the study, provided that the new set date for the study shall be within two weeks of the previously specified date for conducting the postponed or canceled study which formerly sent to Section of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence & Unit of Evaluation of Availability and Bioequivalence Studies of Human Products in Egyptian Drug Authority.

C. In case of the study postponing exceeded two weeks from the date specified for conducting the postponed or canceled study, the approved list of participating volunteers in the study sent by the center shall be cancelled, then those volunteers will be allowed to participate in any other study after obtaining an approval by the Department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority. The aforementioned rules relevant to notifying the Department of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the new date of conducting the bioequivalence studies shall be applied.

(8) In case of conducting a (pilot study), the aforementioned rules and requirements shall be adhered to.

(9) The Department of Protocols Evaluation and Following-up of the Centers of Bioavailability and Bioequivalence - Unit of Evaluation of Bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of conducting Comparative in-vitro as follows:

- The Center shall notify **Department** of Protocols Evaluation and Following-up of the Centers of Bioavailability and Bioequivalence - Unit of Evaluation of Bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the date of conducting each study separately and in sufficient time, before initiating the study, via the department's e-mail,

provided that the center shall be committed to send the product data for which the Comparative in-vitro will be conducted **as follows**:

- Test Product Name & Dosage Form,
- Active Ingredients(s), and
- Manufacturer & License Holder.

Noting that the center may not initiate the study until ~~after~~ fulfilling all of the product documents for which the study will be conducted, as aforementioned indicated.

- In case of postponing or cancellation of the study, the Section of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence & Unit of Evaluation of Availability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of that postponing or cancellation in sufficient time, via the e-mail of the Section of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence & Unit of Evaluation of Availability and Bioequivalence Studies of Human Products.

(10) **The Section of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence & Unit of Evaluation of Availability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of the date of analyzing of the samples withdrawn for bioavailability and bioequivalence studies (Analysis) as follows**:

- The Center shall notify the Department of Protocols Evaluation and Following-up of the Centers of Availability and Bioequivalence - Unit of Evaluation of Availability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the date of analyzing of the samples withdrawn for bioavailability and bioequivalence studies (Analysis), within a period not less than two working days, via the unit's e-mail, provided that the center must be committed to send the data of this study **as follows**:
- Test Production Name & Dosage Form,
- Active Ingredient (s), and
- Manufacturer & License Holder.

Second: The regulating rules of the work in the centers conducting bioavailability and bioequivalence studies:

(1) The organizational structure members in the center must be as follows:

A. The center manager, the technical manager and the quality assurance manager must attend during conducting of the studies.

B. The analysis manager must attend during analysis of studies.

C. The physician and responsible person for collecting samples must be present during period of the volunteers' attendance at the center.

D. In the emergency cases only, the center manager, technical manager, quality assurance manager or analysis manager may delegate a member of the center's organizational structure to carry out the work on his behalf. One of the aforementioned managers also may delegate a member outside the organizational structure based on a written authorization, provided that the delegated person shall be at the same scientific level, and the number of authorizations should not exceed one authorization per day, otherwise the study must be postponed to another date.

E. The center manager, the technical manager, the quality assurance manager and the analysis manager are permitted to hold only one position for each, and none of them may hold another position in addition to his original work.

F. When making any change in the center's organizational structure, the center shall review the regulating rules of licensing the centers conducting the bioavailability and bioequivalence studies with regard to the organizational structure, then the department of Protocols Evaluation and Following-up of the Centers of bioavailability and Bioequivalence - Unit of Evaluation of bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority shall be notified of any changes. The new members' documents shall be entirely submitted, which include: the appointment contract, CV, obtained certificates, updated organizational structure and an acknowledgment on the center's stationary to work full-time at the center, before starting the work at the center.

(2) An acknowledgment of the volunteers' participating in bioavailability or bioequivalence studies (Consent Form):

A. All of the participating volunteers shall be notified of the entire important information in the internal leaflet of the product under study, which includes: side effects, contraindications, drug-drug interactions, warnings… etc., as well as they shall be informed of all steps of conducting the study and the volunteers' rights.

B. The acknowledgement of the volunteer's participation in bioavailability or bioequivalence studies shall be written in Arabic stating the study data.

C. Each volunteer must have his own acknowledgement, containing the aforementioned data.

D. The volunteer shall sign the acknowledgement before (not during or after) conducting the study.

E. The responsible members of the center shall sign the acknowledgements.

(3) <u>Health status report of the volunteers participating in bioavailability or bioequivalence studies (Case Report)</u>:

A. Each volunteer must have his own health status report and the selection of volunteers must be in accordance with the aforementioned Selection Criteria, including (Demographic Data).

B. The case report shall be written before (not during or after) conducting the study.

C. The report must be signed by the center's physician.

D. The results of all tests conducted on volunteers shall be written by the center's physician.

E. The full (Medical History) of each volunteer shall be presented.

F. The results of the pregnancy test shall be written for the volunteers.

G. (Drugs of Abuse Test) results of the volunteers shall be written.

(4) Laboratory analyzes of the volunteers participating in the study (Laboratory Data).

A. Each volunteer must have his / her own Laboratory test results.

B. All of the analyzes results must be written on the original stationary of the laboratory contracting with the center conducting the analyzes, provided that

they shall be signed and stamped by the laboratory officer and state the (Reference Ranges) of each test.

C. All of the analyzes must be conducted no more than three months before starting the study.

4. The analyses must include the following:

A. Complete Blood Picture and Blood Group.

B. Complete Urine Analysis Report.

C. **Biochemical Data**:

- Fasting Blood Sugar

- **Kidney Function**:

(Serum Urea & Serum Creatinine).

- Liver Function:

(Serum GPT "ALT" & Serum GOT "AST").

- Lipid Profile:

(Total Cholesterol & HDL & LDL & Triglycerides).

D. Serology:

(HIV & HCV).

E. The (kits) of testing (drugs of abuse), (blood kits) for (pregnancy) testing, as well as the (kits) of testing hepatitis "C" (HCV) shall be available, provided that some volunteers shall be tested randomly in the presence of a representative of the Department of Protocols Evaluation and Following-up of the Centers of Bioavailability and Bioequivalence - Unit of Evaluation of Bioavailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority.

(5) Study Protocol:

The study protocol shall be fully prepared, dated and signed by the center's officials and representatives of the company owning of the product before initiating the study, **provided that it shall include the following data**:

- Protocol Approval (signed & dated).

- Test & Reference Products Data:

(The reference product used should be the innovator, and a copy of the website mentioning the used innovator should be attached, otherwise, there must be an approval of the Committee of the Evaluation of Bioequivalence Studies to use this reference product).

- **Half Lives of Analytes to be measured:**

(Calculation of washout period & sampling time intervals should depend on the higher range limit of the half-life of API (s) or its metabolite whenever needed).

- Washout period.
- Date of Volunteers Screening.
- Randomization Plan.
- Dates of Phase I & Phase II.
- Study design & Protocol Illustration and Justification.
- Time and Frequency of Sampling.
- Dosage Form Administration.
- Inclusion & Exclusion Criteria.
- Subjects' Disposition.
- Procedures to Minimize Risk.
- Type of Obtained Biological Samples.
- Storage Conditions of Biological Samples.
- Data Analysis (Pharmacokinetic & Statistical Analysis).
- Template of Informed Consent Form.
- Template of Case Report.
- Protocol Deviation & Justification (To be fulfilled if present).
- Complementary In-Vitro Dissolution Testing Methodology.

(6) Approval of the study protocol by the Scientific Research Ethics Committee (Ethics Committee and/or IRB Approval):

- The approval of the Scientific Research Ethics Committee must include the product name on which the study was conducted, provided that it shall be dated and signed by all members of the Committee before initiating of the study.

(7) <u>Records of samples withdrawals for volunteers participating in the study (Log Book i.e., Sample Time Interval sheets)</u>

A. All of the samples collected for all volunteers participating in the study shall be recorded in samples withdrawal records.

B. The (phase) and (stage) of the study shall be determined in each record.

C. The records must be dated and signed by the person responsible for samples withdrawals.

D. All volunteers participating in the study must sign after each withdraw.

E. Each withdraw must contain the (Real Time) and the time specified in the protocol (Sample Time Interval) for each withdraw from each volunteer.

(8) <u>The labels of the samples tubes withdrawn from volunteers participating in the study</u>:

A. The name or code of the bioavailability or bioequivalence study shall be written.

B. The volunteer number shall be written.

C. The (phase) and (stage) of the study shall be written .

D. (Sample Time Interval) shall be written.

E. These tubes shall be kept in an organized and tidy manner in the (Deep Freezer -80°C).

(9) <u>Measuring the vital signs of volunteers participating in the study (Vital Signs Sheet)</u>:

A. The (Vital signs) of the volunteers participating in the study shall be measured for each (Phase) at each (stage) of the study,

B. They shall be written, signed and dated by the center's physician.

C. The following must be measured:

- Blood Pressure.

- Pulse rate.
- Temperature.

In addition to conducting an examination of all volunteers, including the following:

- Chest, Abdomen Examination… etc.

(10) Recording the side effects in case of emerging on the volunteers participating in the study (Side Effects / Adverse: Reactions Sheet):

A. The side effects emerging on the volunteers participating in the study shall be monitored and recorded for all study phases in addition to establishing a plan to treat the volunteer.

B. The side effects shall be written, signed and dated by the center's physician.

C. In case of emerging side effects on a volunteer that affect the study (for example: vomiting), the study shall be stopped for that volunteer and he shall be excluded from the study.

D. In case of emerging any serious side effects, an emergency plan shall be followed to rescue the volunteer quickly.

(11) Plan of random selection of the participating volunteers (Randomization Plan Sheet):

A. It is necessary to write a plan of random selection of the participating volunteers (randomization plan sheet) for all volunteers participating in the study.

B. The study name or code must be indicated.

C. It must be signed and dated by the center officials.

Third: General rules:

1) The bioequivalence studies are not allowed to be conducted before attendance of all volunteers according to the number mentioned in the study protocol based on the (Sample Size) calculations. In case of uncompleted number, the center can conduct (Add-on Study), provided that the rules organizing this procedure shall be followed, knowing that the latter case is not allowed in case of (Replicate Design) studies. In the event of violation, the Specialized Scientific Committee for Evaluating Bioavailability and Bioequivalence Studies study shall not accept to evaluate the study.
2) The rules of the (GCP) shall be committed, so that the number of beds shall match the number of volunteers to participate in the study.
3) The center shall be committed to inform the Department of Protocols Evaluation and Following-up of the Centers of Biovailability and Bioequivalence - Unit of Evaluation of Biovailability and Bioequivalence Studies of Human Products of the names of volunteers having positive results for (HCV, HIV & Drugs of abuse).
4) The Center shall be committed to destroy the samples (Biological Samples: Plasma, Blood, Urine… etc.) of the studies that have been approved by the Bioavailability and Bioequivalence Studies Evaluation Committee, within a week of the study's approval letter being issued to the Center and in case of violation the necessary measures shall be taken against the center.
5) The center shall be obligated to inform the Department of Protocols Evaluation and Following-up of the Centers of Biovailability and Bioequivalence - Unit of Evaluation of Biovailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority of the places in which the biological samples (Plasma, Plasma, Blood, Urine… etc.) are stored inside the center and any change in the method and locations of preservation as well as the method used to destroy the samples in details.
6) The center is committed to prepare and print the entire file of the (Bio-analytical Method Validation Report) along with (Representative Chromatograms) before starting to analyze the Biological Samples: Plasma, Blood, Urine… etc.)
7) The center shall be committed to conduct a Complementary Comparative In-Vitro study, before starting the clinical phase of the study.
8) The samples withdrawn from all of the volunteers participating in the bioavailability or bioequivalence studies must be kept in the (Deep Freezer -

80°C) until beginning of the analysis procedure. For the (Retained Samples) after the analysis, they must be kept in the (Deep freezer -80°C or -20°C), to be re-analyzed, when necessary, provided that proving the validity of the stability of those samples based on the stability study conducted at the center until obtaining the approval of the study by the Bioavailability and Bioequivalence Studies Evaluation Committee.

9) A full copy of the final study file (Study Report) for bioequivalence or Comparative In-vitro Dissolution Study must be kept, that include all of documents related to each study (Raw Data) (accompanied with all of the documents related to the generic product on which the study was conducted, as well as all the external packages of the generic and reference products on which the study was conducted) in an appropriate manner for a period of not less than five years after the approval date of the study by the Bioavailability and Bioequivalence Studies Evaluation Committee, so that it can be obtained upon request.

10) In case of conducting a bioequivalence or Comparative In-vitro Dissolution Study and the generic product appear to be not equivalent to the reference product, the Center shall send an informing report thereon to the Department of Protocols Evaluation and Following-up of the Centers of Biovailability and Bioequivalence - Unit of Evaluation of Biovailability and Bioequivalence Studies of Human Products in Egyptian Drug Authority.

11) All of the correspondence and requests shall be on the center's stationary, signed by the center director, dated and stamped with the center's seal, and they shall be sent via the department's e-mail:

Hdr.bioequivalence@edaegypt.gov.eg

Only in Sunday of every week from 8 am to 3 pm.

5. References

5-1-Egyptian Guidelines for Bioequivalence Studies For Marketing Authorization of Generic Products(V3).

6. Accessories

6-1-Egyptian Guidelines for Bioequivalence Studies For Marketing Authorization of Generic Products(V3).

6-2 -(checklist)

The requirements that must be met during the periodic following-up visits to bioequivalence centers