Republic of the Philippines
Department of Health
FOOD AND DRUG ADMINISTRATION

6 March 2015

FDA CIRCULAR
No. 2015-003

SUBJECT: **Guidelines on the Implementation of New Rules and Regulations on the Licensing of Sponsors and Contract Research Organizations (CROs) following Administrative Order No. 2014-0034, dated 13 October, 2014.**

I. RATIONALE

The conduct of clinical trial is one of the most critical and complex components in the drug development process. The management of clinical trials in all phases should take into account two important aspects: the protection of the rights, safety and well-being of the subjects or patients, and the credibility and integrity of the clinical trial data obtained.

With a steady and substantial increase in the number of establishments involved in clinical trials, there is a need for appropriate monitoring and regulation to ensure that these two aspects are met. It is in this context that the Food and Drug Administration (FDA) has required the licensing of these establishments.

On 13 October 2014, Administrative Order No. 2014-0034 was issued to (a) update and streamline regulatory approaches in licensing of drug establishments, (b) provide faster access of drug products to the public; and (c) promote transparency through the universal use of electronic transaction.

In line with the new rules and regulations on the licensing of establishments classified as sponsors or CROs, FDA hereby prescribes the requirements for the applications for initial and renewal issuance of License to Operate (LTO), variations, as well as other guidelines relevant to these establishments.

II. DEFINITION OF TERMS

Definition of terms shall follow the definitions provided for under Administrative Order No. 2014-0034. In addition, the following terms are hereby defined:

1) Clinical Trial Protocol – a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

2) Good Clinical Practice (GCP) – a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
3) Investigator – a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
An investigator may also refer to an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving a subject.

III. GENERAL GUIDELINES

A. All local sponsors and CROs conducting local clinical trials for purposes of drug registration must secure an LTO from the FDA.

B. No clinical trial of a foreign sponsor may be conducted in the country unless an FDA-licensed CRO takes up the responsibility for the foreign sponsor.

C. Other licensed drug establishments (e.g. manufacturer, importer, or distributor) desiring to engage in clinical trials as either a sponsor or CRO must secure the appropriate LTO.

D. Entities engaged in the following trial-related duties and functions delegated by a sponsor are required to secure an LTO as CRO:
1) Oversight (e.g. ensuring quality assurance and/or quality control systems are in place to ensure clinical trials are conducted, data is gathered, and subsequently reported)
2) Management of clinical trials
(a) development of protocols and/or trial design;
(b) selection of investigator(s) and/or site(s);
(c) screening and/or recruitment of subjects;
(d) data handling (e.g. collection, analysis/evaluation, and record keeping)

Entities involved in the procurement/importation, storage, and/or distribution of investigational product(s) are not required to secure an LTO as CRO, unless they are involved in other activities mentioned above. These entities must follow other existing licensing requirements.

E. Accredited bioequivalence testing centers need not apply for LTO as Sponsor or CRO.

IV. LICENSE TO OPERATE (LTO) APPLICATIONS

A. *Documentary Requirements*

1) Application Form

A completely filled-out and notarized application form signed by the owner/authorized representative must be submitted.

2) Proof of Business Name Registration

A valid proof of business name registration must be submitted:

(a) For single proprietorship - Certificate of Business Registration issued by the Department of Trade and Industry (DTI)

(b) For corporation, partnership and other juridical person - Certificate of Registration issued by the Securities and Exchange Commission (SEC) and Articles of Incorporation

(c) For government-owned or controlled corporation - the law highlighting the provision creating such establishment

The proof of business name registration must specify the exact and complete address, e.g., unit number, floor, building, lot, block, phase, street, barangay, city/ municipality, province, where applicable.

3) Credentials of Qualified Person

The Certificate of Attendance to basic and advanced GCP courses of the identified qualified person must be submitted.

Other credentials of the qualified person as proof of qualification will not be submitted during application but may be verified during inspection.

4) Risk Management Plan

A general risk management plan (RMP) for the establishment must be submitted. The RMP shall contain details on how to identify, characterize, prevent or minimize risk relating to the IP they engage with. These shall include pharmacovigilance activities and interventions of the establishment to manage the risks.

5) Location Plan

A sketch of the location of the establishment must be submitted which shall be used for inspection purposes. This sketch must indicate clear directions with identified landmarks to locate the establishment.

In addition, the Global Positioning System (GPS) Coordinates in decimal degrees (DD) [Latitude and Longitude] must be indicated in the submission.

6) Proof of Payment

Proof of payment (e.g., official receipt or authorized bank payment slip) must be included as proof of filing of application.

7) Self-assessment Toolkit
To guide and facilitate the submission, a Self-Assessment Toolkit (SATK) must be submitted, which will also serve as the worksheet during evaluation of FDA.

The list of documentary requirements for initial and renewal applications of LTO, reissuance of lost or destroyed LTO, as well as voluntary cancellation is attached as Annex A.

B. *Evaluation of Application*

All applications shall be reviewed to determine compliance with the administrative and technical requirements.

The FDA in the course of its evaluation may require additional or supplemental documents that will show proof of compliance to the existing regulations.

C. *Post-licensing Inspection*

All sponsors and CROs with approved LTO shall be subjected to routine inspection for their compliance to Good Clinical Practice (GCP) and other relevant and applicable standards in relation to their licensed activity (e.g. Good Distribution and/or Good Storage Practices [GDP and GSP]). In addition, major variation applications may require post-licensing inspection prior to the approval of such variation. Sponsors and CROs which are subject to regulatory action due to different triggers (e.g., violation of any of the provisions of FDA laws, rules and regulations, and any other laws related thereto, occurrence of adverse drug reactions, as well as other quality, safety, and/or efficacy issues) shall also be inspected.

In addition to the documentary requirements submitted during application (Section IV, A of this Circular), the following documents shall be verified during inspection:

- Quality Management System
- Quality Manual and Standard Operating Procedures
- Delegation of Authority and other relevant agreements (e.g. between local and foreign sponsor)
- Credentials of Qualified Person
- Proof of Ownership/Lease Agreement of the space/building by the establishment occupied
- Relevant reference materials (e.g. FDA laws and regulations, latest editions of International Conference on Harmonisation [ICH] Safety and Efficacy Guidelines, Philippine National Health Research System [PNHRS] -National Ethical Guidelines for Health Research, GDP and GSP, and others)

The abovementioned additional documents will serve as proof of compliance by the establishment with the existing regulations on licensing.

A report shall be issued to the drug establishment after inspection, which shall be the basis for further decision/action of FDA (e.g., approval/ disapproval of an application for LTO, and/or for such other purposes).

Compliance with cold-chain management is also required for sponsors and CROs utilizing vaccines, biologics, and other temperature-sensitive products.

Clinical trial sites, sponsors and CROs are subject to inspection at any time with or without prior notice.

D. *Application for Variation*

The following are the applicable variations to an approved LTO as sponsor or CRO:

1) Major Variation
   (a) Change of Ownership
   (b) Transfer of Location
2) Minor Variation – Prior Approval
   (a) Additional Activity
   (b) Expansion of Establishment
   (c) Change of Business Name
   (d) Zonal Change in Address
   (e) Change of Delegated Sponsor Activities
3) Minor Variation – Notification
   (a) Change of Qualified Person

FDA should be duly informed of any changes to the approved LTO, whether or not these are classified as variations described above. Other changes may also be added to the variations mentioned, which shall be subject of an appropriate regulation.

The list of documentary requirements for the abovementioned variations is attached as Annex B.

All variations are subject to the existing variation/amendment fee, except for transfer of location which is subject to initial payment for two (2) years validity of LTO.

Sponsors and CROs applying for minor variations may continue business operations provided that an application for such variation has already been filed.

E. *Accessibility*

All electronic fillable forms shall be made accessible at the FDA website.

V. RESPONSIBILITIES OF QUALIFIED PERSON

A qualified person within the organization of the licensed establishment must be identified. The qualified person must be in charge of the overall operations of the establishment which shall include:

1) Monitoring/supervision of all operations of the establishment;
2) Observance of Good Clinical Practice, as well as other applicable international best practices;
3) Ensuring that all clinical trials have satisfactorily complied with the requirements of the ethics committee, as well as other relevant government agencies;
4) Ensuring any adverse drug reactions/events experienced by subjects/patients are properly handled, documented, and reported to FDA; and
5) Ensuring compliance of the establishment with existing regulations.

The abovementioned responsibilities should be properly translated into a Standard Operating Procedure (SOP) which shall be duly validated during post-licensing inspection.

VI. SUSPENSION, REVOCATION, OR CANCELLATION OF THE LTO

Depending on the impact of violation to GCP, the suspension, revocation or cancellation of the LTO of sponsors or CROs shall mean the deferment or disapproval of clinical trial application/s, and/or suspension, revocation, or termination of approved clinical trial/s with consideration to subject/patient safety and compensation within the scope of ICH GCP.

LTO suspension, revocation or cancellation does not preclude initiation of legal proceedings against a sponsor, CRO or any qualified person in the establishment.

VII. RESPONSIBILITIES OF IMPLEMENTING OFFICES

Consistent with the regulatory powers provided under (3), c, Sec. 2, Article III, Book I of the implementing rules and regulations of Republic Act No. 9711, FDA and its Regional Field Offices through the Director General may call on the assistance of any department office and/or government agency for the effective implementation of its rules and regulations.

In addition, Local Government Units (LGUs) are enjoined in monitoring licensed sponsors and CROs in their localities for their compliance to the existing laws and their respective rules and regulations. Any violation found by the LGU inconsistent with the FDA rules and regulations shall be reported to FDA for regulatory action.

VIII. TRANSITORY PROVISIONS

Considering the preparations from both FDA and the industry, all existing sponsors and CROs may apply until 30 June 2015 for LTO without violation.

IX. REPEALING CLAUSE/SEPARABILITY CLAUSE

Provisions of previous FDA circulars and memoranda that are inconsistent with this issuance are hereby withdrawn, repealed, and/or revoked accordingly. In case any part, term or provision of this FDA Circular is declared contrary to law or unconstitutional, other provisions which are not affected remain in force and effect.

X. EFFECTIVITY

This Circular shall take effect upon approval and signature by the FDA Director General.

ATTY. NICOLAS B. LUTERO III, CESO III
OIC-Director IV
OIC, Food and Drug Administration

ANNEX A

LIST OF DOCUMENTARY REQUIREMENTS FOR SPONSORS AND CONTRACT RESEARCH OGANIZATIONS LTO APPLICATIONS

A. Initial LTO Application
   1) Application Form
   2) Proof of Business Name Registration
   3) Credentials of Key Personnel
   4) Risk Management Plan
   5) Location Plan
   6) Proof of Payment (e.g. official receipt or authorized bank payment slip)
   7) Self-Assessment Toolkit

B. Renewal LTO Application
   1) Application Form
   2) Copy of Certifications issued as a result of LTO Variation
   3) Proof of Payment (e.g. official receipt or authorized bank payment slip)
   4) Self-Assessment Toolkit

C. Reissuance of Lost or Destroyed LTO
   1) Letter of Request
   2) Affidavit of Loss or Destruction
   3) Proof of Payment (e.g. official receipt or authorized bank payment slip)

D. Voluntary Cancellation of LTO
   1) Letter of Request
   2) Original LTO

ANNEX B

LIST OF REQUIREMENTS FOR VARIATION APPLICATIONS FOR SPONSORS AND CONTRACT RESEARCH ORGANIZATION

A. Major Variations

Change of Ownership	
C	There is a change of ownership of the drug establishment licensed.
D	1. Application Form 2. Proof of business name registration reflecting the name of new owner 3. Deed of sale or transfer of rights of ownership 4. Updated Delegation of Authority (where applicable) 5. Proof of payment 6. Self-Assessment Toolkit

Transfer of Location	
C	1. Physical transfer of the drug establishment with changes in the previously approved address. 2. Other variations (e.g. change of key person and/or business name) may also be included as long as the variation is noted in the application and the corresponding requirements for such changes are included. The payment remains as initial fee, regardless of the additional variation.
D	1. Application Form 2. Proof of business name registration reflecting the new address 3. New Location Plan 4. Updated Delegation of Authority (where applicable) 5. Proof of payment 6. Self-Assessment Toolkit

B. Minor Variations – Prior Approval

Additional Activity	
C	1. Shall refer to an additional activity engaged by the CRO (e.g. Oversight with additional development of protocol and/or design activity) 2. Shall also refer to a change from the initially approved activity (e.g. data handling to oversight).
D	1. Application Form 2. Contract Agreements to prove activity 3. Proof of payment 4. Self-Assessment Toolkit

Expansion of Establishment	
C	1. Shall refer to the expansion made which is adjacent to the existing location of the establishment. 2. Expansion shall also include additional floors where the building is occupied
D	1. Application Form 2. Proof of payment 3. Self-Assessment Toolkit

Change of Business Name	
C	1. Change only in the business name 2. No transfer of location or change of ownership.
D	1. Application Form 2. Proof of business name registration reflecting the new name of the drug establishment 3. Proof of payment 4. Self-Assessment Toolkit

Zonal Change in Address	
C	Shall refer to change of the name/number of the street/building without physical transfer of the establishment.
D	1. Application Form 2. Document issued by the local municipality as proof of zonal change 3. Proof of payment 4. Self-Assessment Toolkit

Change of Delegated Sponsor Activities	
C	Shall refer to addition or deletion of any delegated sponsor-related clinical activities.
D	1. Application Form 2. Updated Delegation of Authority 3. Contract Agreements to prove activity/ Termination of contract or conformance letter (where applicable) 4. Proof of payment 5. Self-Assessment Toolkit

C. Minor Variations – Notifications

Change of Qualified Person	
C	There is a change (whether addition, replacement) in the initially identified qualified person with no change of delegated sponsor activity.
D	1. Application Form 2. Credentials of Qualified Person 3. Proof of payment 4. Self-Assessment Toolkit