ORIGINAL ARTICLE

A Feasibility Study on Re-establishing the Bioavailability/Bioequivalence Unit of the Department of Pharmacology and Toxicology, College of Medicine-University of the Philippines Manila

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ABSTRACT

Objectives. The Bioavailability/Bioequivalence Unit (BA/BE Unit) of the Department of Pharmacology and Toxicology, College of Medicine, University of the Philippines Manila which has not been operational since 2012, is due for renewal of its accreditation. To date, there are only three Philippine Food and Drug Administration-accredited laboratories that perform bioequivalence studies in the Philippines. One of the prerequisites of registering specific generic medicines is the conduct of Bioequivalence (BE) studies which are performed to ensure that the generic drug is at par with the innovator drug. Thus, this study aimed to determine the feasibility of re-establishing the BA/BE Unit as a bioequivalence testing center.

Methods. The feasibility study done is a qualitative descriptive analysis based on expansive literature review and performance of SWOT analysis within the BA/BE unit. Literatures were selected based on its assessed relevance to the study. The databases checked were PubMed and Google Scholar. The terms used were from the Medical Subject Heading (MeSH) including feasibility studies, therapeutic equivalency, and generic drugs. Literature review was performed on the factors affecting the four types of feasibility studies (market, technical, financial, and organizational). A SWOT analysis of the BA/BE Unit was done through the review of records and documents of previous BE studies and focus group discussion among the BA/BE Unit team members.

Results. The BA/BE Unit conducted 24 bioequivalence studies from 2006-2009 and still receives inquiries from drug companies. It implements its QMS throughout the pre-analytical, analytical, and post-analytical stages of the workflow. Its organizational structure consists of qualified professionals with updated GCP and GLP certificates. Because of the adequately equipped facility, lower honoraria for government-employed personnel, and lower expenses for laboratories and in-patient admissions, the cost of conducting a bioequivalence study in the BA/BE Unit will be lower than in other BE centers.

Conclusion. Based on the SWOT analysis and market, technical, financial, and organizational considerations, re-establishing the BA/BE Unit as a bioequivalence testing center is feasible.

Keywords: feasibility studies, therapeutic equivalency, generic drugs

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INTRODUCTION

The price of medications is one of the reasons contributing to rising healthcare costs. Generic medicines, which are therapeutically equivalent to innovators, are suitable, equally efficacious, safe, and inexpensive alternative medications. One of the prerequisites for registering specific generic medicines is the conduct of Bioequivalence (BE) studies. BE studies are performed to ensure that the generic drug is at par with the innovator drug. Bioequivalence studies assume that two products are bioequivalent when there is no significant difference in the rate and extent of absorption of the test product as compared to the reference drug.[1] They serve as surrogate markers for clinical safety and efficacy of generic products in place of clinical trials.

As specified under Food Drug and Administration (FDA) regulation (21 CFR 320.24), bioavailability and bioequivalence testing must use the most accurate, sensitive, and reproducible method appropriate to the test products. Table 1 shows the test procedures that are considered adequate in bioavailability (BA) measurement and bioequivalence establishment, in order of preference: pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, comparative clinical trials, and *in vitro* studies.[2] PK studies are the most preferred way of assessing the BA/BE of drug products since drug levels can be easily measured through accessible biological fluids such as blood or plasma.

Figure 1 illustrates the process of review for New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). In NDA, a submission must include chemistry, manufacturing and controls, non-clinical pharmacology and toxicology, human pharmacokinetics and BA, and clinical safety and efficacy trials.[1] In contrast, an ANDA submission for generic drugs must include comparable sections of NDA including a BE study but without the need for nonclinical and clinical safety and efficacy studies.[3] The reduced cost in this abbreviated approval process means that generic drugs can be given at lower prices.

The PFDA strictly follows the Association of Southeast Asian Nations (ASEAN) and World Health Organization (WHO) guidelines in the implementation of bioequivalence regulation and registration.[4,5] These drug product registration guidelines require BE studies to be done for generically equivalent drug products to assure uniformity in the quality of pharmaceutical products.

The PFDA is the regulatory body responsible for the approval, oversight, and inspection of facilities that conduct BE studies. The main objective in the approval or certification of the facility before the performance of BE studies is to prove that the facility complies with the principles of Good Clinical Practice (GCP) and Good Laboratory Practices (GLP). Table 2 summarizes the initial checklist of requirements of the PFDA in the application for inspection of the Bioequivalence Testing Center and documents to be assessed during the inspection proper.[6]

To date, there are only three PFDA-accredited laboratories performing BE studies in the Philippines. With the limited laboratories in the country and the increased demand for BE studies, the PFDA allows drug companies to have their BE studies done in other countries if the PFDA requirements are complied with. However, BE studies outside the country are costlier. With the increasing local manufacturers of generic products, BE testing centers are unable to completely cope with the demand. Another preferable and better option for this problem will be to increase the number of BE testing centers locally. Aside from creating more jobs and economic growth, these will mean more affordable but of similar efficacy and quality drugs available to the public. Improving access of the public to cheaper, safer, and good quality drugs is consistent with the Sustainable Development Goal (SDG) 3 on good health and well-being set by the United Nations General Assembly in 2015.[7]

The Bioavailability/Bioequivalence Unit (BA/BE Unit) of the Department of Pharmacology and Toxicology, College of Medicine, University of the Philippines Manila is one of the existing BE testing centers in the Philippines. However, it is still due for renewal of its accreditation by the PFDA and has not been operational since 2012. The last inspection by the PFDA of the BA/BE Unit was on November 22, 2012. The critical findings in the official inspection report issued in July 22, 2014 included (1) the absence of established quality management system which would cover all critical operations

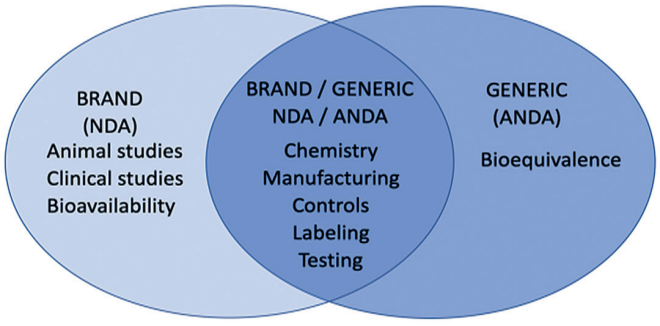

Figure 1. New Drug Application (NDA) vs Abbreviated New Drug Application (ANDA) Review Process.

Table 1. Bioequivalence Study Test Methods

Test Method	Type	Parameters/Endpoints	Sample Size	Cost
PK Studies	*In vivo*	PK parameters such as AUC, C_{max}, T_{max}	Small	+++
PD Studies	*In vivo*	Pharmacologic or therapeutic effect	Small	+++
Comparative Clinical Trial	*In vivo*	Therapeutic effect	Large	+++++
In vitro Studies	*In vitro*	Physicochemical Parameters / Drug release	N/A	+

Table 2. Documentary Requirements for Philippine FDA Accreditation as BE Testing Center

Requirements for Application for Inspection	Requirements for Application for Inspection and During Inspection Proper	Requirements During the Inspection Proper
1. Letter of request 2. Proof of payment 3. Facility floor plan 4. List of key personnel of the BE testing center 5. List of SOPs, work instructions, forms 6. List of facilities, equipment, and instruments available at the BE testing center for the clinical and/or bioanalytical phase of the study 7. Summary document on the changes initiated by the BE testing center since the last FDA inspection for accreditation purposes (in terms of organization, personnel, facilities, operations, etc.) (for renewal applications)	1. Organizational chart 2. Certificates of accreditation and Licenses-to-Operate from relevant agencies 3. Quality manual 4. Personnel records including curriculum vitae and training records demonstrating sufficient qualifications based on educational background, training, and work experience 5. Standard Operating Procedures (SOPs), work Instructions, and forms for all critical processes and activities including interim activities during the COVID-19 pandemic 6. Records/logbook of instrument and equipment usage, maintenance, calibration, and standardization 7. Records of environmental monitoring and control (e.g., temperature, relative humidity, pests, microbes) 8. Memoranda of Understanding/ Contracts of Agreements between the BA Unit and: a. Duly licensed/accredited 3rd party Screening Laboratory (for hematology, urinalysis, X-ray, ECG, drug testing, etc.) b. Duly licensed/accredited 3rd party Bioanalytical Facility c. Other relevant parties involved in biological sample transport, waste disposal, instrument calibration, maintenance, and standardization 9. List of BE Studies completed for the past accreditation period and/or schedule of ongoing and future studies 10. Study specific documents (where applicable), including but not limited to: a. Protocol (final version) and amendment/s b. Template of the subject informed consent form(s) and amendment(s) c. Template of Case Report Forms (CRF) d. Investigator's brochure, update(s), Summary of Product Characteristics (SPC) or package insert, where applicable e. Clinical trial report (final) with tables and listings f. List of subjects involved in the study g. Monitoring plan and visit reports, if applicable h. Validation protocol and report for the bioanalytical method/s i. Analytical method procedure, study plan, and report j. Description of the processing of pharmacokinetic samples k. Data management and validation plan, if applicable l. Statistical analysis plan	1. Full Report of at least 2 most recently completed bioequivalence studies for renewal applications 2. Other relevant documents in fulfillment of applicable principles of Good Clinical (GCP) and Good Laboratory Practices (GLP)

of the BA/BE Unit, (2) absence of a dedicated area for the clinical part of the study including screening and consent-taking processes, and (3) the possibility and risk of mix-ups and contaminations in the set-up in the laboratory prior to its renovation, in case there will be simultaneous activities like BA/BE-related analytical activities and research by students and faculty. Although the BA/BE unit was commended for having employed competent and appropriately trained personnel for its clinical facility, the BA/BE Unit was recommended not to pursue further BE studies unless the critical findings have been addressed.

Thus, this research aimed to determine the feasibility of re-establishing the Bioavailability/Bioequivalence Unit (BA/BE Unit) of the University of the Philippines College of Medicine Department of Pharmacology and Toxicology (UPCM DPT) Bioanalytical and Toxicology Laboratory as a bioequivalence testing center. Specifically, this research analyzed the strengths, weaknesses, opportunities, and threats to the BA/BE Unit and determined the market, technical, financial, and organizational feasibility of re-establishing the BA/BE Unit as a BE testing center.

MATERIALS AND METHODS

Search Strategy

An expansive literature review was done to identify possible sources of data. The search terms used were feasibility studies, therapeutic equivalency, and generic drugs. The databases checked were PubMed and Google Scholar. Literatures were selected based on its assessed relevance to the study. Data from previous studies performed within the unit were compiled and reviewed. Selection of data to be reported in the study was based on the confidentiality agreement between the unit and the requesting party. Specific information cannot be divulged in the paper.

Study Design and Data Processing

The feasibility study done used qualitative descriptive analysis based on expansive literature review and performance of SWOT analysis within the BA/BE unit. A SWOT analysis of the BA/BE Unit was done through a review of records and documents of previous BE studies and focus group discussion (FGD) among the BA/BE Unit team members. For the FGD, all the participants were invited. Verbal consent of each participant was secured prior to the FGD.

There were 13 BA/BE Unit team members who participated in the SWOT analysis and FGD: eight faculty members (four associate professors, three professors and one professor emeritus) from the Department of Pharmacology and Toxicology, College of Medicine – UP Manila, two university researchers from the Bioanalytical and Toxicological Laboratory of the Department of Pharmacology and Toxicology, College of Medicine – UP Manila, two faculty members (one professor and one professor emeritus) from the Department of Physical Sciences and Mathematics of the College of Arts and Sciences of UP Manila, and one university researcher from the Research and Analytical Services Laboratory (RASL) of the College of Arts and Sciences of UP Manila. The FGD was done virtually using Zoom which was recorded and later transcribed.

The SWOT analysis included sorting out the data into four categories: strengths, weaknesses, opportunities, and threats. The strengths and weaknesses were the internal factors within the organization, while the opportunities and threats originated from external factors.[8] During the SWOT analysis, data was gathered individually from the members of the FGD. All submitted data were then individually assessed and validated. The final transcriptions of the Zoom recording were done by two members of the research team and were compared, reviewed, and approved by the members of the research group.

Extensive literature review was done on the different factors affecting the types of feasibility studies including (1) market feasibility; (2) technical feasibility; (3) financial feasibility; and (4) organizational feasibility.[9]

Ethical Clearance

The study has been granted exemption from ethics review by the UP Manila Research Ethics Board (UPMREB 2022-0471-EX).

RESULTS

SWOT Analysis

Analysis of the strengths and weaknesses of the BA/BE Unit plus the opportunities and threats was done by the team to assess whether the project was achievable and feasible. The framework used in the focus group discussion of the SWOT analysis was the elements of the QMS: Organization (O), Personnel (P), Facilities and Safety (F & S), Equipment (E), Purchasing and Inventory (P & I), Process Control (PC), Information Management (IM), Documents and Records (D & R), Occurrence Management (OM), Process Improvement (PI), Customer Satisfaction Survey (CSS). The latest SWOT analysis of the BA/BE Unit last August 31, 2022, is summarized in Table 3.

Strengths

The BA/BE Unit with the support of the administration of the UP system has an efficient organization of competent and appropriately trained personnel. The BA/BE Unit is composed of faculty and staff who are well-versed in both GCP and GLP which are prerequisites for conducting bioequivalence studies and who are experts not only in conducting BA/BE studies but also in conducting other types of clinical trials.

In its continued quest for excellence, the BA/BE Unit is committed to delivering superior quality but affordable services through the strict implementation of its existing QMS (quality manual) and up-to-date clinical and laboratory SOPs. To demonstrate their commitment, the BA/BE Unit has provided a newly renovated facility that is dedicated mainly to BE studies. This facility is fully furnished with equipment that will support the operation of BA/BE Unit such as chemical fume hoods, freezers, ovens, rotary evaporators, centrifuges, sonicators, volumetric wares, general laboratory glasswares, analytical balances, and the main analytical equipment which is the Ultra High Liquid Chromatograph equipped with Variable Wavelength Detector.

To further increase the capability of the BA/BE Unit in conducting the bioanalytical phase of the bioequivalence study, the BA/BE Unit is in collaboration with the Research and Analytical Services Laboratory (RASL) of the College of Arts and Sciences of UPM.

For the clinical phase of the bioequivalence study, the BA/BE Unit is in partnership with local communities to facilitate recruitment of study volunteers. Furthermore, the BA/BE Unit is in collaboration with the Philippine General Hospital (PGH) for the diagnostic screening of the volunteers/study participants and the use of their clinical facility during the implementation of the BE studies.

Weaknesses

Despite the existing strengths of the BA/BE Unit, there were also several identified weaknesses which are mostly related to financial aspects and resources. Firstly, which is strongly agreed by the group is the lack of fiscal autonomy of the BA/BE Unit in the use of funds. For continued compliance with GCP and GLP, the BA/BE Unit has to perform calibration and maintenance of facility and equipment regularly, however, funds for this activity are lacking. If funds are available, on the other hand, the bureaucratic paperwork within the UP System would cause delay in the processing of documents, especially in the procurement of reagents, supplies, equipment, and services. This bureaucratic paperwork also causes delay in the release of funds for the compensation of personnel.

The Unit and the collaborating college also lacks regular chemists and other technical personnel, and has a high turnover rate for contractual personnel which is mostly due to non-competitive compensation and benefits for the regular position and the delay of the release of compensation for the non-regular personnel.

In terms of information management, the BA/BE Unit lacks a secured dedicated intranet database for patients/

volunteers, and digitized laboratory results and case report forms. It is also noted that for the previous BE studies, the satisfaction and expectations of the customers or stakeholders regarding the services rendered by the Unit were not monitored and evaluated.

Opportunities

Several opportunities for improvement of the BA/BE Unit were identified. First, the BA/BE Unit can render services to different stakeholders because of the ASEAN harmonization that recommends strict implementation of BA/BE studies on generic products. Second, the BA/BE Unit can collaborate with different colleges and units within the university such as UPM Information Management System and UPM Math and Computer Science Unit of the Department of Physical Sciences and Mathematics, College of Arts and Sciences for the improvement of data management. This and together with the fact that the market

Table 3. Strengths, Weaknesses, Opportunities, and Threats (SWOT) Analysis of the BA/BE Unit

STRENGTHS

Organization
- With efficient organization of competent and appropriately trained personnel
- With strong commitment to the delivery of superior quality but affordable services
- With existing high quality management system (quality manual)
- With updated clinical and laboratory SOPs
- With support from the administration of the UP system
- With partnership with local communities to help in the recruitment of volunteers

Organization, Equipment, Facility, and Safety
- With collaboration with the Philippine General Hospital for the diagnostic screening of the volunteers/study participants and the use of their clinical facility during the actual conduct of the study
- With collaboration with the College of Arts and Sciences of UP Manila for the analytical phase of the BE study
- With newly renovated facility with an area dedicated mainly for BE studies
- With fully furnished laboratory set-up with the required calibrated equipment for BE studies

Personnel
- With exceptional faculty and staff who are well-versed in both GCP and GLP, who have previous experience in doing BE studies and who are experts in conducting other clinical trials

WEAKNESSES

Organization
- Lacks fiscal autonomy

Personnel
- Delayed processing of financial documents within UP Manila System
- Lacks regular chemist and other technical personnel employed by the department and collaborating Units

Equipment
- Lacks funds for calibration and maintenance

Purchasing and Inventory
- Delayed procurement process (e.g., reagent, supplies, equipment)

Information Management, Documents, and Records
- Lacks digital case report forms
- Lacks database of patient/volunteers
- Lacks database for lab results
- Lacks secured dedicated intranet database for the Unit

Occurrence Management, Purchasing, and Inventory, Customer Satisfaction Survey
- Lacks evaluation of previous BE studies

OPPORTUNITIES

Organization
- Collaboration with the different colleges and units within the university for data management: NIHCT, UPM IMS, Math and Computer Science Unit of the Department of Physical Sciences and Mathematics College of Arts and Sciences
- Doubling of the market share of local manufacturers and increased use of generic (both branded and unbranded) in the Philippine pharmaceutical market which increases the demand for the conduct of BE studies
- Possibility of Industry-academe partnerships
- ISO/IEC accreditation

Personnel
- Opportunities for personnel training services

Facility
- There are only a limited number of FDA-approved BA/BE testing centers in the country
- New clinical trial facility in the National Institutes of Health (NIH) to house the study participants or venue for the clinical phase of the BA/BE study

Facility and Equipment
- Access to sources of funds for additional state-of-the-art laboratory equipment

Process Control
- ASEAN harmonization provides guideline that recommends the strict implementation of BA/BE studies on generic products

THREATS

Organization
- Importation of generic medicines with bioequivalence studies conducted in the country of origin, particularly from India
- Lower-priced generics from India

Personnel
- Brain drain

Facility and Safety
- Competition with local and international bioequivalence testing centers

Process Control
- Reciprocity in the ASEAN harmonization since BA/BE tested generics from ASEAN-member countries will no longer need BA/BE testing if tested in the country of origin

share of local manufacturers (both branded and unbranded) in the Philippine Pharmaceutical market has doubled in previous years and is projected to further increase, increases the demand for the conduct of BE studies and increases the demand for other BE testing centers.

Other aspects that were considered as opportunities for expansion and improvement of the laboratory are the possibility of the use of the new clinical trial center in the National Institutes of Health for the clinical phase of the BA/BE studies, access to various sources of funds for additional state-of-the-art laboratory equipment, the possibility of having industry-academic partnerships, advancement of the skills of the personnel through internally and externally provided training, and obtaining the ISO/IEC 17025 accreditation to further showcase the system and capability of the laboratory in terms of bioanalytical testing.

Threats

Threats recognized are mainly due to the local and international competition of bioequivalence testing centers. Due to the ASEAN harmonization, the BA/BE tested generics from ASEAN-member countries will no longer need BA/BE testing in the Philippines if the products were already tested in the country of origin. In addition, the BA/BE Unit will also lose its opportunity to render services to importing companies, particularly for imported generic medicines from India, since the BA/BE studies conducted from the country of origin for the imported generic medicines are acceptable.

Types of Feasibility Studies

Factors assessed in each type of feasibility study are listed in Figure 2.[9,10]

1. Market Feasibility

a. Potential market

One of the requirements in registering generic products is BE study. The concept of bioavailability and bioequivalence study in the Philippines was first adopted through Administrative Order No. 67 s. 1989 on Revised rules and regulations on registration of pharmaceutical products. With the increase of many off-patent pharmaceutical products coming from various manufacturers in the market, the PFDA expanded the coverage of the BA/BE requirement. Table 4 summarizes the evolution of BA/BE study requirements. Looking at the last row in Table 4, the potential market will be the manufacturers of those listed generic drugs.

b. Market competition

Currently, there are only three laboratories approved by the PFDA to perform bioequivalence studies. These are (1) Center of Excellence in Drug and Research, Evaluation and Studies, Inc. (CEDRES); (2) Pharmalytics Corporation; and (3) Center for Biopharmaceutical Research of De La Salle Medical and Health Sciences Institute. Due to ASEAN harmonization, PFDA imposed stricter compliance with BA/BE requirement. However, due to the limited number

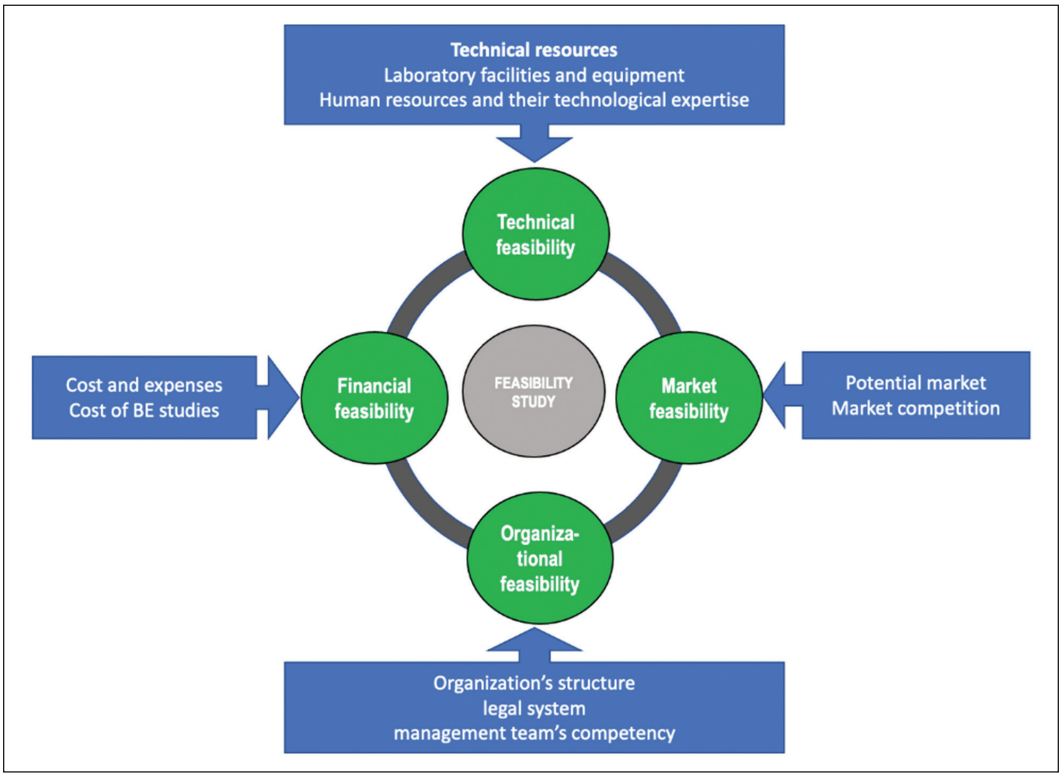

Figure 2. Four types of Feasibility Studies.

Table 4. Regulations on Bioavailability and Bioequivalence

Regulatory Document	Date of Implementation	Drugs requiring BA/BE study
Administrative Order No. 67 s. 1989	March 15, 1989	Not specified[11]
Administrative Order no. 41 s. 1994	December 20, 1994	List B "Prime" drugs[12]
Bureau Circular No. 01 s. 1997	January 21, 1997	List B "Prime" drugs[13]
Bureau Circular No. 13A s. 1999	June 14, 1999	Rifampicin only[14]
Bureau Circular No. 008 s. 2006	June 01, 2006	Rifampicin, Atenolol, Diltiazem, Gliclazide, Metformin, Metoprolol, Nicardipine, Nifedipine, Phenytoin, Propranolol, Pyrazinamide, Theophylline[15]
FDA Circular No. 2013-014	July 01, 2013	Rifampicin, Atenolol, Diltiazem, Gliclazide, Metformin, Metoprolol, Nicardipine, Nifedipine, Phenytoin, Propranolol, Pyrazinamide, Theophylline, BCS class IV drugs[16]
FDA Circular No. 2013-014	January 01, 2014	Rifampicin, Atenolol, Diltiazem, Gliclazide, Metformin, Metoprolol, Nicardipine, Nifedipine, Phenytoin, Propranolol, Pyrazinamide, Theophylline, BCS class IV drugs, BCS class II drugs not eligible for biowaiver, generic products of off-patent innovator drugs, modified-release oral preparations[16]
FDA Circular No 2016-019	October 25, 2016	Rifampicin, Atenolol, Diltiazem, Gliclazide, Metformin, Metoprolol, Nicardipine, Nifedipine, Phenytoin, Propranolol, Pyrazinamide, Theophylline, BCS class IV drugs, BCS class II drugs not eligible for biowaiver, generic products of off-patent innovator drugs, modified-release oral preparations, drugs with narrow therapeutic index, fixed-dose combinations with at least one API requiring BA/BE study[16]

of accredited testing centers in the Philippines, FDA also accepts BA/BE studies performed outside the country given that the BA/BE study site conforms to GCP and GLP.

2. Technical Feasibility

A fundamental requirement in the conduct of bioequivalence studies is to follow the GLP and GCP thus, it is imperative that a QMS must be in place.[17] The ASEAN Mutual Recognition Arrangement for Bioequivalence Study Reports of Generic Medicinal Products provides guidelines and references necessary to establish the QMS of the laboratory.[18] Paid and free awareness and trainings for GLP and ISO/IEC 17025:2017 are also available to provide the personnel with the basic knowledge in creating the QMS which can be prepared by any of the qualified personnel of the laboratory preferably with a strong background in clinical or analytical testing.

a. Laboratory facilities and equipment

The BE study must be conducted under conditions that will provide adequate safety for the subjects. The site for the BE must have adequate clinical and analytical facilities, including appropriate equipment. Collection of the biological specimen is conducted in the clinical facilities during the clinical phase of the study while the analytical facilities analyze the collected biological specimens for the bioequivalence study of drug and/or metabolite concentrations.[19] For the clinical phase of the study, this can be done on the establishment of the CRO or in suitable sites in a hospital. Table 5 shows the areas/rooms that should be included for the clinical part of the BE study.[17]

The analytical facility must comply with the requirements of GLP (e.g., OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring & ISO/IEC 17025). As stated in the ISO/IEC 17025:2017, the laboratory "shall have access to equipment (including, but not limited to measuring instruments, software, measurement standards, reference materials, reference data, reagents, consumables or auxiliary apparatus)."[20] The equipment shall be adequate in its design and function for the generation, measurement, or assessment of data and facility environmental control according to the written standard operating procedures.[19]

Table 5. Areas for Clinical Phase of the Bioequivalence Study

- Subjects' registration and screening
- Obtaining informed consent of individual subjects without compromising privacy
- Subjects' housing
- Subjects' recreation
- Pharmaceutical operations (restricted access room, e.g., for storage, repacking, dispensing, documentation)
- Administration of the investigational products and sample collection
- Sample processing (e.g., plasma separation) and storage (freezer)
- Controlled access storage of study materials, medication, and documentation including CRFs
- Preparation of standardized meals and a dining hall
- Proper care of subjects who require emergency or other medical care, with emergency or first-aid equipment and appropriate medication for use in emergencies
- Archiving

Higher Education Institutions that offer science and allied health-related courses especially those that are offering graduate studies are required to be equipped with laboratory facilities that will cater to the experiments of the students to fulfill the requirements of the curriculum. Furthermore, laboratories equipped with liquid chromatographs with UV detector can be used to analyze pharmaceutical products.[21-23]

b. Human resources and their technological expertise

Adequate and qualified personnel must also be available for the timely and proper conduct of the study.[23] The overall responsibility for the clinical conduct of the study is assigned to the principal investigator who is selected by the CRO. These duties include designing the protocol, administration of the products under investigation, coordinating with local authorities and the ethics committee, and developing the final study report.[17] Services of other technical personnel including chemists/analysts, chemical technicians, pharmacist, physician, nurse, phlebotomist are availed only during the actual experimentation of the study.

For colleges and universities with chemical laboratories, chemist and chemical technicians are available to guide the students in the conduct of experiments and operation of analytical instruments. They already have the necessary skills and training in handling the basic instrument required to conduct the bioanalytical phase of bioequivalence studies.

Table 6. Capital and Operating Expenses in Setting up a BE Facility in Malta

Operating expenses EUR 131,000 yearly	Materials	EUR 27,000
	Rent of premises	EUR 25,000
	Salaries	EUR 79,000
Capital expenses EUR 254,000	Equipment	EUR 219,000
	Furniture	EUR 35,000
Total Cost	Set up cost and 1st year	EUR 385,000

Table 7. Responsibilities of CRO

1. Ensure that the principles of GCP and GLP, as appropriate, are complied with in the CRO
2. Ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study
3. Ensure the maintenance of a record of the qualifications, training, experience, and job description for each professional and technical individual
4. Ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions
5. Ensure that appropriate and technically valid SOPs are established and followed, approve all original and revised SOPs, and ensure the maintenance of a historical file of all SOPs
6. Ensure that there is a quality assurance (QA) program with designated personnel and assure that the QA responsibility is being performed following the principles of GLP and GCP, as appropriate
7. Ensure that an individual is identified as responsible for the management of the archive(s), and ensure that the documents
8. Ensure that an individual is identified as responsible for the management of the archive(s), and ensure that the documents transferred to the archives are kept under adequate conditions for the appropriate duration
9. Ensure that supplies meet requirements appropriate to their use in a study
10. Establish procedures to ensure that computerized systems are suitable for their intended purpose, and are validated, operated, and maintained following the principles of GCP and GLP, as appropriate.

3. Financial Feasibility

a. Capital and operating expenses

To set up a bioequivalence testing center, the initial expenses of institutions with existing laboratories and analytical equipment will be towards the calibration and preventive maintenance of equipment, training of personnel, method development/validation, laboratory supplies, and FDA accreditation. On the other hand, laboratories without a liquid chromatographic system such as LC-UV may need to invest at least Php 4 to 7 million for an LC system with quaternary solvent delivery system.[24-27] In addition to the MOOE, other expenses would include the salaries for the personnel services and the contingency and administrative overhead.

A study in Malta that investigated the feasibility of setting up a local independent facility for bioequivalence testing showed that all eight companies that they interviewed outsourced BE studies to Indian laboratories.[28] The computed total cost of setting up amounted to 385,000 euros (Table 6).

b. Estimated cost per bioequivalence study

According to a report on the Cost of Generic Drug Development and Approval, the estimated cost of pivotal BE study on healthy volunteers is around $2,000 or Php 100,000 per subject for simple small molecule drugs.[29] For a standard BA/BE study two-sequence, two-period (2x2) crossover design involving 24 participants, the estimated cost is $48,000 or Php 2.4M.[3] In the Philippines, estimates may vary from Php 2M to 4M depending on the laboratory, the drug to be tested, and the study design.[30]

Organizational Feasibility

Legal system

The contract research organization (CRO) involved in the conduct of *in vivo* studies or the analysis of samples or data from *in vivo* studies, must comply with the existing national requirements for its legal status.[17]

Management team's competency

CRO is the scientific organization to which the sponsor may transfer some of its tasks and obligations. Table 7 outlines the minimum requirements for CRO management.

An organizational chart outlining the key positions and the names per position should be provided by the CRO. This chart must be dated, authorized, and updated regularly. An adequate roster of eligible, trained, and experienced medical, paramedical, technical, and clerical staff is needed to support the conduct of the study. A job description per position including the responsibilities should be provided, signed, and dated. The responsibilities of all personnel are defined in the SOP. A file folder of the study staff includes the staff curriculum vitae (CV), current registration certificates, and other relevant documents as proof of competency. Prior to

participation in the study, staff orientation, training, and periodic competency assessment (initial, and annually, onwards) are conducted. Documentation of all activities related to study staff/personnel is strictly observed. All of these are in accordance with Annex 9 on the guidance for organizations performing *in vivo* bioequivalence studies.[17]

DISCUSSION

BA/BE Unit

The BA/BE Unit was established with the mission to conduct reliable, rapid, and high-quality BA/BE studies with conformance to current local and international standards and guidelines, thus ensuring the quality, safety, and efficacy of drug products that are made available to the Filipino people.

Unfortunately, after the FDA inspection in 2012, the Audit Team required the BA/BE Unit to undertake a Trial Bioequivalence Study covering all relevant clinical and bioanalytical activities before it can continue to conduct BE studies. This was a big drawback to the BA/BE Unit since it had no budget for a trial BE study. After numerous meetings and dialogues with PFDA, the BA/BE Unit was subsequently allowed to perform a validation study on methods development, instead of doing the trial BE study. This quasi-research has been approved by the UP Manila Research Ethics Board (UPMREB) and has received a funding grant from the Emerging Interdisciplinary Research (EIDR) Program of the Office of the Vice President for Academic Affairs.

SWOT Analysis

Considering all the strengths, weaknesses, opportunities, and threats enumerated in Table 3, the members of the BA/BE Unit developed some strategies (Table 8) to overcome and avoid the weaknesses of the BA/BE Unit and the threats to it.

The most immediate strategy that needs to be done is the renewal of the accreditation by the Philippine FDA. At present, the BA/BE Unit has applied for inspection and re-accreditation by the PFDA. The initial list of requirements in Table 2 has been submitted to them and the documents to be assessed during the inspection proper are already prepared.

Market Feasibility of the BA/BE Unit

The BA/BE Unit was able to perform 24 BE studies in 4-5 years. In the last few years, there was a consistent increase in the demand and inquiries from several drug companies regarding the performance of BE studies by the BA/BE Unit.

Technical feasibility of the BA/BE Unit

Aside from the required research, all corrective/preventive actions, and recommendations from the PFDA for the improvement of the Unit were subsequently addressed; the most important of which were the creation of the quality management system and the renovation of the UPCM DPT Bio-analytical and Toxicology Laboratory. The new laboratory was designed to have different areas for the Bioanalytical Unit, the Analytical Unit, Bioavailability/Bioequivalence Unit, and Animal Research facility.

Table 8. Strategies for the Advancement of the Unit

STRATEGIES FOR ADVANCEMENTS/ **future quadrant/LONG-TERM** (How can we best employ our strength to take advantage of the opportunities in front of us?) 1. Implementation of Customer Satisfaction Survey and process improvement 2. Continuing education of personnel 3. ISO/IEC accreditation 4. Access to sources of funds for additional state-of-the-art laboratory equipment	STRATEGIES TO OVERCOME WEAKNESS/ **internal fix-it/SHORT-TERM** (How can we use opportunities to overcome the weakness?) 1. Collaboration w/ other colleges and units for information management
STRATEGIES TO AVOID THREATS/ **External Fix-it/ SHORT-TERM** (How can we use our strength to avoid our threats?) 1. Facilitate FDA re-accreditation of the Unit urgently 2. Advertise BE services (e.g., social media, brochures, email blasts, fliers, and pamphlets) 3. Strategic planning for expansion and diversification	STRATEGIES TO AVOID AND OVERCOME WEAKNESS AND THREATS/ **Survival** (How can we minimize our weaknesses and manage the threats?) 1. Renewal of accreditation 2. Forge stronger partnerships with potential stakeholders

At present, the BA/BE Unit implements its QMS throughout the pre-analytical, analytical, and post-analytical stages of workflow. The QMS adapted is based on the model developed by Clinical and Laboratory Standards Institute (CLSI) and is fully compatible with ISO, OECD-GLP, and ICH-GCP. The strategies on how to maintain the critical operations of the BA/BE Unit and how to assure accuracy and reliability throughout the conduct of the testing are provided in the quality manual.[3]

The BA/BE Unit has been consistently made up of faculty and personnel of the Department of Pharmacology and Toxicology who are all knowledgeable in GCP and GLP. Although the BA/BE Unit's laboratory facilities were admittedly lacking in the last inspection and audit of PFDA in 2012, the recently renovated, highly-equipped, and updated laboratory was designed to facilitate satisfactory conduct of BE studies with its own analytical unit and without interference with the other laboratory activities of the Department. In addition, the BA/BE Unit is in collaboration with the RASL for the performance of the analytical phase of the BE study.

Both BA/BE Unit and RASL have access to the equipment needed by a laboratory as per the requirements of ISO/EIC 17025:2017 as summarized in Table 9. Both laboratories also include qualified faculty and personnel who have training in both GCP and GLP. Table 10 enumerated the qualifications and expertise of those involved in the BE studies.

Table 9. Summary of Equipment Available in the UPCM DPT Bio-analytical and Toxicology Laboratory Bioavailability/Bioequivalence (BA/BE) Unit and the Research and Analytical Services Laboratory (RASL) of the College of Arts and Sciences (CAS) of UPM

	Available Equipment in UP Manila's BA/BE Unit	Available Equipment in UP Manila CAS RASL
Analytical equipment	Waters™ Acquity UPLC H-system pH meter Shimadzu TW223L Analytical Balance Mettler Toledo Analytical Balance Tanita Weighing Scale Electronic Balance Mdl WT	Shimadzu Nexera RP-HPLC System Shimadzu AUX 220 Analytical Balance
General equipment	Labwe BT5R Refrigerated Centrifuge Thermo Scientific Clinical Centrifuge BD Clay Adams Centrifuge Thermolyne Vortex Mixers IUCHI ITS3B Magnetic Stirrer Drying oven Waterbath Magnetic stirrer Hot plate Freeze Dryer Vacuum Pump Rotary Evaporator	Hettich Universal 320R Refrigerated Centrifuge Fisher Scientific Vortex Mixer Rocker Sonicator Water Bath Hot Plate with Magnetic Stirrer Drying Oven Simplicity Ultrapure Water Dispenser Vacuum Pump Rotary Evaporator
Cold storage equipment	Refrigerator Walk-in Freezer Walk-in Chiller	-40°C Freezer -80°C Bio Freezer
Environment monitoring and safety equipment	Chemical Fume Hood Autoclave Thermohygrometers	Chemical Fume Hood Autoclave

Aside from the dedicated area and equipment for the analytical part, the newly renovated BA/BE Unit has an assigned area of adequate size for the subject holding, screening, and examination room, containing pulse oximeter, stethoscope, digital sphygmomanometer, infrared forehead ther-mom-eter, and calibrated height and weight measuring scale.

Table 10. List of Qualifications of Faculty and Personnel from the UPCM DPT Bio-analytical and Toxicology Laboratory Bioavailability/Bioequivalence Unit and the Research and Analytical Services Laboratory (RASL) of the College of Arts and Sciences of UPM

	N
Doctor of Medicine / principal investigator (1 professor emeritus, 5 professors, 6 associate professors)	14
PhD in Health Sciences (Social Sciences) / principal investigator	1
PhD in Molecular Biology and Biotechnology / co-investigator	1
Doctor of Public Health (Medical Microbiology / co-investigator	1
Doctor of Materials Engineering / co-investigator	1
MSc in Clinical Trials / principal investigator	1
MSc in Biochemistry / co-investigator	1
Registered chemist (1 professor emeritus, 1 professor, 3 university researchers)	5
Registered pharmacist (2 co-investigators, 2 as pharmacists during the conduct of the study)	4
Registered medical technologist (university researcher)	1
Laboratory technician	1
Laboratory aide	1

Financial Feasibility of the BA/BE Unit

Aside from the grants from the UP System, once the BA/BE Unit gets its renewal, it can resume its operation and provide services to the government and private clients. This will generate income to support the facility and further expand other research and service activities. The consistent inquiries and demand from different drug companies for BE studies would make the BA/BE Unit sustainable in the future.

Since there is already an existing adequately equipped laboratory facility and equipment, there is no need for capital expenses. In addition, since most of those involved in the study received their salaries from government universities, the expenses for honoraria will be less since there is a limit to what can be given to government employees based on the Department of Science and Technology, (DOST) salary rates. In addition, the collaboration with PGH makes the expenses for the screening laboratories and in-patient admissions cheaper and reasonable.

Although the costs from other private bioequivalence centers cannot be stated here due to confidentiality, considering all the factors mentioned above, the total cost of conducting a bioequivalence study will be competitive and lower than that of private BE testing centers. Table 11 describes the general cost of a BA/BE study in 2004-2006.

The total cost of each bioequivalence study is divided into (a) supplies and materials (50%), (b) laboratory and analytical tests (20%), (c) quality control tests (10%), (d) participant remunerations (10%), and (e) professional services (10%). A preliminary bioequivalence study takes two months to complete, while a full-fledged study takes four months. The

Table 11. Bioequivalence Studies from 2004-2006[31-34]

Drug	Type of Study	Year	Amount
Rifampicin Chewable Study	Bioequivalence Study	2004	Php 987,500
Rifampicin Suspension	Preliminary Bioequivalence Study	2005	Php 200,000
Rifampicin Suspension	Bioequivalence Study	2005	Php 950,000
Rifampicin Capsule	Bioequivalence Study	2005	Php 990,000
Rifampicin Suspension	Bioequivalence Study	2006	Php 950,000

BA/BE unit received 2-3 products for testing each year from 2003-2006. Specific details on previous studies cannot be disclosed due to confidentiality agreement between the unit and the requesting parties.

Organizational Feasibility of the Unit

The BA/BE Unit is located at the Department of Pharmacology and Toxicology, 3rd floor, Salcedo Hall, UPM College of Medicine Building. The Department was set up in 1912 to support the aims of the Department to be "a leader in the discipline of pharmacology and toxicology, conducting research and providing extension services that contribute to the improvement of quality of healthcare in the country."[35]

The organizational structure consists of a team of qualified and trained professionals who have updated GCP and GLP certificates (Table 10). The BA/BE Unit is under the UPM system. It is collaborating with the RASL for the analytical part and with PGH for the clinical part, including the laboratories needed for the screening processes and the in-patient admission during the actual conduct of the study. Figure 3 shows the organizational structure of the BA/BE Unit of the Bioanalytical and Toxicology Laboratory and its working relationship with RASL and PGH.

Figure 4 sums up the different factors evaluated in the BA/BE Unit based on the different types of feasibility studies.

Limitations of the Findings

Assessment of the feasibility of establishing a bioequivalence testing center was limited to SWOT analysis, market, technical, financial, and organizational feasibility, in an academe setting. There was only one FGD which was limited to the BA/BE Unit team members.

CONCLUSION

Based on the market, technical, financial, and organizational considerations, re-establishing the Bioavailability/Bioequivalence Unit of the Department of Pharmacology and Toxicology Bioanalytical and Toxicology Laboratory of the College of Medicine, University of the Philippines Manila as a bioequivalence testing center is feasible. For

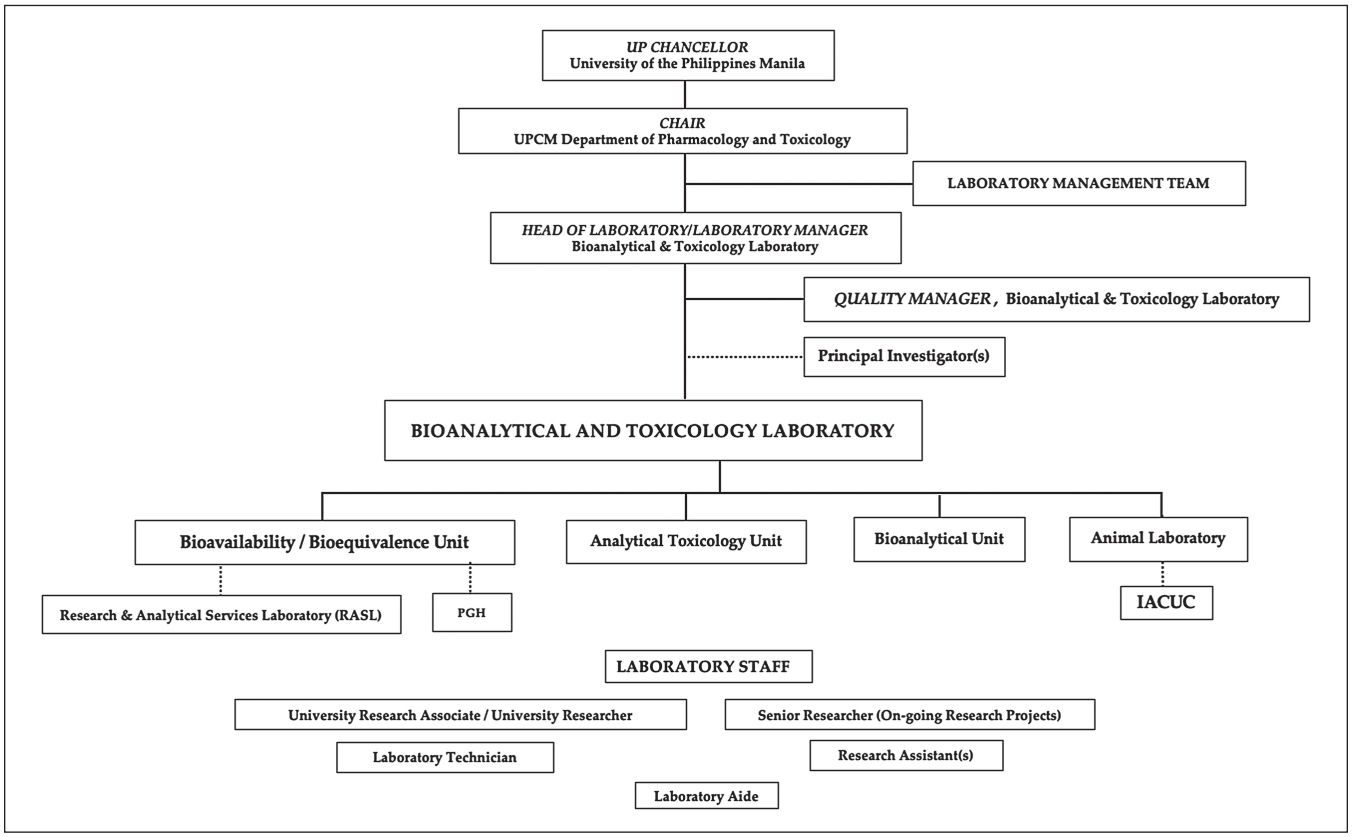

Figure 3. UPCM DPT Bioanalytical Laboratory Organization Structure.

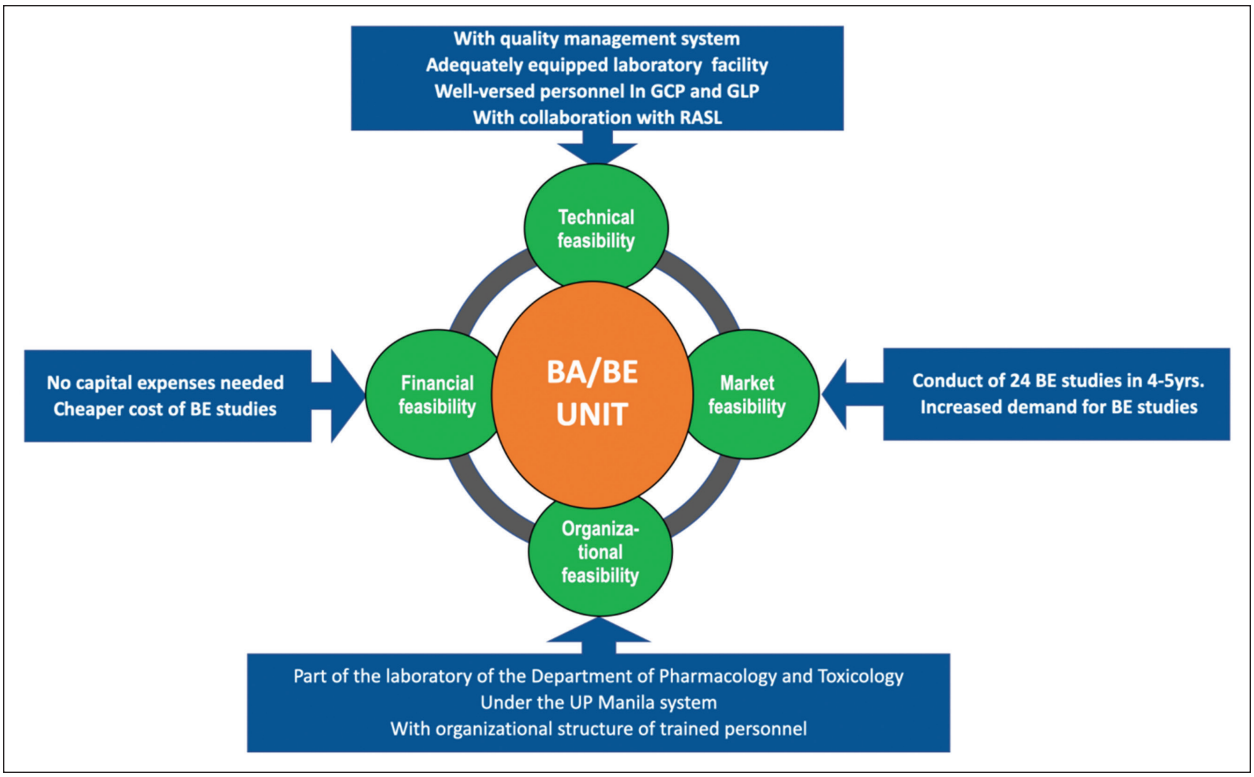

Figure 4. Different feasibility studies on establishing BA/BE Unit.

the market feasibility, there is a consistent increase in the demand and inquiries from several drug companies regarding the performance of BE studies by the BA/BE Unit. For the technical and financial feasibility areas, despite the weaknesses and threats that have been identified, the BA/BE Unit is furnished with adequate facilities and laboratory equipment complimented by qualified faculty and staff who have received GCP and GLP training; these strengths would meet the opportunities of growing demand for BE studies. In addition, the organizational structure of the BA/BE unit being under the UP system and the collaboration with both RASL for the analytical part and with PGH for the clinical part would mean less overhead expenses and more affordable costs of BE studies than the private testing centers.

Disclaimer

Views expressed in this article are from the authors and not an official position of the institution.

Statement of Authorship

LAEC contributed in conceptualizing the research protocol, consulting or collaborating with colleagues in the scientific or academic community to which she belongs and seeking advice from authoritative bodies possessing expertise in ethical, legal, social and other issues that the researcher may encounter throughout the research process, obtaining ethical approval of the protocol, and for cooperation with the REC in the conduct of the study, applying for ethical review and approval before the conduct of a research, acquisition and analysis of data, drafting and revising the manuscript, and final approval of the version to be published. ENT contributed in conceptualizing, reviewing of related literature and preparing the research protocol, and preparing the final manuscript for publication. LBP contributed in conceptualizing, reviewing of related literature and preparing the research protocol, preparing the final manuscript for publication, consulting or collaborating with colleagues in the scientific or academic community to which she belongs and seeking advice from authoritative bodies possessing expertise in ethical, legal, social and other issues that the researcher may encounter throughout the research process, and applying for ethical review and approval before the conduct of a research. CAJ contributed in conceptualizing the research protocol, consulting or collaborating with colleagues in the scientific or academic community to which she belongs and seeking advice from authoritative bodies possessing expertise in ethical, legal, social and other issues that the researcher may encounter throughout the research process, obtaining ethical approval of the protocol, and for cooperation with the REC in the conduct of the study. MSFSC and AMY contributed in conceptualizing the research protocol, consulting or collaborating with colleagues in the scientific or academic community to which she belongs and seeking advice from authoritative bodies possessing expertise in ethical, legal, social and other issues that the researcher may encounter throughout the research process. NSQ contributed in conceptualizing

the research protocol. drafting and revising the manuscript, and final approval of the version to be published. LCRP contributed in drafting and revising the manuscript, and final approval of the version to be published.

Author Disclosure

The authors have no real conflict of interest since the researchers' involvement has no direct impact in the results of or conduct of the study. Reflexivity was practiced by the researchers to make sure that assumptions and beliefs will have minimal influence on the research process.

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