NAPM

NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS
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INDIVIDUAL BIOEQUIVALENCE - CLINICAL SIGNIFICANCE, ETHICAL AND COST CONSIDERATIONS

Advisory Committee Meeting for Pharmaceutical Science
September 23, 1999.

My name is Leon Shargel, Ph.D. and I am the Vice President and Technical Director of the National Association of Pharmaceutical Manufacturers, NAPM. I have a B.S. in Pharmacy from the University of Maryland and Ph.D. in Pharmacology from the George Washington University Medical Center. I have authored or co-authored many papers in biopharmaceutics and pharmacokinetics including a leading textbook, now in its 4th edition that is required reading in many colleges of pharmacy.

NAPM is the international trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues concerning the generic pharmaceutical industry.

On behalf of NAPM and its members, including our generic drug product manufacturers and contract research organizations (CROs), I would like to discuss the FDA proposed recommendations for performing individual bioequivalence studies. Specifically, I will consider the clinical significance, ethical concerns and cost considerations for performing these studies.

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INDIVIDUAL BIOEQUIVALENCE - CLINICAL SIGNIFICANCE, ETHICAL AND COST CONSIDERATIONS

Clinical Significance

Fundamental to this discussion is whether switchability is a clinically significant problem with which we need to be concerned.

We certainly agree with the FDA position that "the prescriber and patient should be assured that the newly administered drug product will yield comparable safety and efficacy to that of the product for which it is being substituted." However, we do not agree with FDA that the use of replicate studies and the determination of individual or population bioequivalence is needed or desirable for the determination of bioequivalence.

On January 28, 1998 Dr. Stuart L. Nightingale, Associate Commissioner for Health Affairs wrote a letter to health practitioners that was prompted by concerns about the interchangeability of certain products characterized as narrow therapeutic index (NTI) drug products (Attachment 1). This 'Dear Colleague' letter concluded that:

- Additional clinical tests or examinations by the health care provider are not needed when a generic drug product is substituted for the brand name product.

- Special precautions are not needed when a formulation and/or a manufacturing change occurs for a drug product, provided that the change is approved according to applicable laws and regulations by the FDA.

- As noted in the "Orange Book," in the judgement of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is brand name or generic drug product.

- It is not necessary for the health provider to approach any one therapeutic class of drug products differently from any other class when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

Additionally, Dr. Nightingale wrote that, " To date, there are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand name drug."

More recently, Eric Ormsby of the Health Protection Branch Canada gave a presentation at the AAPS/FDA Workshop on Individual Bioequivalence: Realities and Implementation, Montreal, Canada, 8/30-9/1/99 in which he reported that 2,500 products on the Canadian market were approved using the AB standards. Mr. Ormsby stated in a slide, "Is post-marketing surveillance really so insensitive that clinically important problems can't be detected?" Thus, Mr. Ormsby indicated that the Canadian Health Protection Branch has not observed any clinical safety problems due to switchability.

Therefore, we feel that the determinination of therapeutic equivalence by the current FDA review and approval process for an Abbreviated New Drug Application (ANDA) and for scale-up and post approval changes (SUPAC) is working and that generic substitution of AB rated drug products is safe and efficacious.

What then is the driving force for performing individual bioequivalence studies? Certainly the determination of subject-by-formulation and within subject variability might be useful to know. However, should this information be required for all bioequivalence studies? We think not.

To date, approximately 50 data sets from bioequivalence studies have been statistically analyzed for subject-by-formulation interactions. It is apparent from the IBE Workshop in Montreal and at other meetings (e.g., AAPS Annual Meeting in Boston, November, 1996), that experts disagree considerably as to the clinical significance and interpretation of a subject-by-formulation interaction. It is our opinion that if a subject-by-formulation interaction is a safety or efficacy problem, the scientific literature would be replete with clinical studies or at least case reports showing this problem.

Ethical Concerns

A fundamental caveat in performing clinical research is "Do No Harm." The Declaration of Helsinki, 1989 (Attachment 2) discusses 12 Basic Principles that should be considered when performing research on human subjects. I would like to mention three of these basic principles:

#1 "Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature."

At this time, we do not have scientific literature that indicates that switchability is a safety or efficacy problem.

#2 "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specifically appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed."

With noted exceptions listed in the draft guidance, FDA recommends that all bioequivalence studies be designed as replicate studies and that the applicant may use average population statistics as the basis for establishing bioequivalence. Data from the replicate design will be given to the FDA for further statistical analysis.

It is my understanding that FDA is requesting this information from these replicate studies to further assess the need for and application of the proposed individual individual bioequivalence criterion. We feel that extra data sets from human subjects should not be obtained without a peer reviewed protocol describing how the data is to be analyzed and a risk/benefit assessment.

#4 " Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."

A four-way crossover replicate design has a greater inherent risk to the subjects and double the drug exposure compared to a two-way crossover study. Chances for an adverse drug event are increased proportionately. Moreover, more blood samples are drawn per subject and that may increase the trauma to the subject and risk of damage to the blood vessels.

Cost Considerations:

We feel that an additional financial cost to the pharmaceutical industry is inconsequential if this additional cost burden provides for the marketing of safer and more efficacious drug products. To date, we are not convinced that the added expense and burden to the pharmaceutical industry is justified. The proposal for performing replicate design bioequivalence studies increases the cost to both the finished dosage form manufacturers and to the contract research organizations (CROs).

The cost to the finished dosage form manufacturers is based on two aspects. First, the cost for doing a replicate design study is higher compared to a two-way crossover study. Using three drug classes, warfarin, indapamide and diltiazem, we surveyed several CROs to provide cost estimates (Attachment 3). Each CRO had experience in performing replicate design studies and was given the same experimental design with an appropriate number of subjects that would provide the statistical power needed for generic drug product approval using average bioequivalence. In all cases, the cost for the performing the replicate design study is greater.

Second, the longer time for completing a replicate design study is an added cost to the finish dosage form manufacturers due to the longer time to complete an ANDA application resulting in a longer time before market approval.

Replicate design bioequivalence studies are also an increased burden to the CROs. Some of the problems discussed by our CRO members include:

Recruitment problems

More drop outs are predicted for a 4-way vs 2-way crossover design.

Participants need to be remunerated more for four dose periods.

Participants may be used less frequently due to greater blood volume or longer washout periods. This results in (1) having a smaller subject population pool from which to recruit, (2) using more naive volunteers in the study, or (3) promoting professional volunteers who participate due perhaps to unemployment elsewhere.

Institutional Review Board (IRB)

IRB approval for replicate studies may be a problem based on ethical and risk/benefit considerations

Drug monitoring

More drug monitoring for adverse events is needed (e.g., a replicate design for diltiazem will need more electrocardiogram monitoring.)

Increased clinical capacity

In order to maintain the same number of studies, CROs will have to double their clinical capacity and double the number of available beds.

Longer delays in placing the study in the queue.

According to one CRO, studies might be delayed from 6-12 months. For those drug products in the R & D pipeline, this would result in a longer exclusivity period for the innovator drug product.

Summary:

1. Switchability does not appear to be a clinically significant safety or efficacy problem.

2. The ethics (risk/benefit) for performing replicate design clinical studies for most drugs to assess bioequivalence must be carefully considered.

3. Replicate design clinical studies places an additional burden to the industry

4. Even though product approval is based on average bioequvalence criteria, the extra study data obtained from replicate studies may be used indiscriminately by consumer groups, state formulary commission, and others to determine if the product has a subject-by-formulation interaction and whether the product passes IBE criteria .

Recommendations:

We recommend that a appropriately designed replicate clinical studies be performed to examine the switchability issue. The objectives, statistical design and data analysis should be available for peer review. The funding of these studies should not be an additional burden to the pharmaceutical industry. One possible suggestion for funding, may be through the Product quality Research Initiative (PQRI).

I thank you for the opportunity to discuss our comments. I hope that these comments are clear and welcome any questions that you may have.

ATTACHMENT 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 28, 1998

Dear Colleague:

As you may be aware, certain individuals and groups have appeared recently before state legislatures, state boards of pharmacy, and drug utilization review committees, to express concerns about the interchangeability of certain products they characterize as narrow therapeutic index (NTI) drug products. A particular concern being raised by them is whether the safety and efficacy profile of these products could change if a switch were made from a brand-name product to an FDA-designated therapeutically equivalent generic product. FDA wishes to comment on the issue of interchanging any brand-name drug with a therapeutically equivalent generic drug and requests that you inform your association's members of this information.

For both brand-name and generic drugs, FDA works with pharmaceutical companies to assure that all drugs marketed in the U.S. meet specifications for identity, strength, quality, purity and potency. In approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that the generic drug is interchangeable with the brand-name drug under all approved indications and conditions of use. For these reasons, FDA approved product labeling does not recommend that any additional tests need to be performed by the health care provider when a switch occurs from a brand-name drug product to a generic equivalent drug product, from a generic equivalent to a brand-name product drug, or from one generic product to another when both are deemed equivalent to a brand-name drug product. Brand-name drug products and therapeutically equivalent generic drug products are identified in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," frequently called the "Orange Book."

In addition to tests performed prior to market entry, FDA regularly assesses the quality of products in the marketplace and thoroughly researches and evaluates reports of alleged drug product inequivalence. To date, there are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug. Questions have been raised in the past, as well, regarding brand name and generic products about which there could be concern that quality failures might represent a public safety hazard. FDA has performed post-marketing testing on many of these drugs to assess their quality. In one instance, more than 400 samples of 24 marketed brand-name and generic drug products were tested and found to meet the

established standards of purity and quality. Because patients may pay closer attention to their symptoms when the substitution of one drug product for another occurs, an increase in symptoms may be reported at that time, and anecdotal reports of decreased efficacy or increased toxicity may result. Upon investigation by FDA, no problems attributed to substitution of one approved drug product for another has occurred.

FDA works with both brand-name and generic drug product manufacturers after a drug product is in the marketplace to assure its quality. For example, brand-name and generic drug product manufacturers may want to change the drug formulation, site of manufacture, or manufacturing process after the drug is in the marketplace. These types of changes can be put in place only after the drug manufacturer provides the FDA with sufficient evidence that the drug identity, strength, quality, purity and potency will not change.

There are products in which small changes in the dose and/or blood concentration could potentially result in clinically important changes in drug efficacy or safety. Usually, these drugs require frequent adjustments in the dose of the drug and careful patient monitoring irrespective of whether the drug is a brand or generic drug product. These drugs may sometimes be described in FDA approved drug labeling as narrow therapeutic range drugs.

FDA may recommend to the manufacturers additional tests for approval of both brand-name and generic products, depending on the complexity of a drug substance or drug product and also depending on whether small changes in the dose and/or blood concentration could result in changes in drug efficacy or safety. It may also require additional tests for certain post-approval changes in manufacturing. The agency's recommendation to the manufacturer for these additional tests is designed to give the practitioner and patient additional assurance of product quality and interchangeability. These additional requirements should not be construed to mean that additional clinical scrutiny is necessary when interchange occurs. If anything, the additional tests required of pharmaceutical manufacturers are designed to reduce, not increase, concerns on the part of patients and practitioners.

Based on FDA's determination of therapeutic equivalence between generic and innovator drug products, the FDA concludes that:

- Additional clinical tests or examinations by the health care provider are <u>not</u> needed when a generic drug product is substituted for the brand-name product.

- Special precautions are not needed when a formulation and/or a manufacturing change occurs for a drug product provided that the change is approved according to applicable laws and regulations by the FDA.

- As noted in the "Orange Book," in the judgment of the FDA, products evaluated as therapeutically equivalent can be expected to have equivalent clinical effect whether the product is brand name or generic drug product.

- It is not necessary for the health care provider to approach any one therapeutic class of drug products differently from any other class, when there has been a determination of therapeutic equivalence by FDA for the drug products under consideration.

In considering drug product selection decisions, FDA acknowledges and supports the importance of good communication between the patient and the health care provider, particularly with regard to medications that require frequent monitoring of performance. We hope this information is useful to health care providers when making decisions regarding drug product selection.

We thank you for seeing that this information reaches the members of your organization.

Sincerely,

Stuart L. Nightingale

Stuart L. Nightingale, M.D.
Associate Commissioner
for Health Affairs

ATTACHMENT 2

International Ethical Guidelines for Biomedical Research Involving Human Subjects

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

Geneva
1993

Annex 1

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians
in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians

should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers — either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

ATTACHMENT 3

September 16, 1999

Leon Shargel, Ph.D.
National Association of Pharmaceutical Manufacturers
320 Old Country Road
Garden City, NY 11530-1752
VIA FAX (516) 741-3696

Dear Leon:

Enclosed please find sample budgets for the six abstracts which were previously sent to you.

Drug Name	2-way	4-way
Warfarin	$111,267.00	$318,056.00
Indapamide	$ 99,304.00	$214,353.00
Diltiazem	$154,119.00	$334,682.00

If you require further information or have any questions, please do not hesitate to contact us.

Cordially,

CRO

DRAFT BIOAVAILABILITY STUDY DESIGN FOR NTI

for

Client – Generic Mfg.

Study Template No. 01

Test Product:	Warfarin
Reference Product:	COUMADIN® 2 mg Tablet by Dupont Pharma
Dosing:	1 x 2 mg tablets
Study Overview:	Randomized, single-dose, two-way crossover design under fasting conditions
Study Participants:	Young, healthy males (18-45 year old inclusive) N = 24 Confinement: Approximately 10 hours prior to until 24 hours after dose administration.
Screening requirements:	**General**: Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations**: CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation**: Drug abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 21 samples per subject per period Predose (0 hour) and after dosing at .167, .33, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24, 48, 72, 96, 144, 192, 240 hours.
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing as determined by the investigator(s); Blood glucose will be monitored prior to dose administration and after dosing as determined by the investigator(s).
Analytical Method:	HPLC

CRO
DRAFT BIOAVAILABILITY STUDY DESIGN
for
Client – Generic Mfg.

Study Template No. 02

Test Product:	Indapamide
Reference Product:	LOZOL® 2.5 mg Tablets by Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Dosing:	1 x 2.5 mg
Study Overview:	Randomized, single-dose, two-way crossover design under fasting conditions
Study Participants:	Young, healthy males (18-45 year old inclusive) N = 26 Confinement: Approximately 10 hours prior to until 24 hours after dose administration.
Screening requirements:	**General:** Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations:** CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation:** Drug abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 19 samples per subject per period Predose (0 hour) and after dosing at .25, .5, .75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72 hours.
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing as determined by the investigator(s); Blood glucose will be monitored prior to dose administration and after dosing as determined by the investigator(s).
Analytical Method:	HPLC

CRO

DRAFT BIOAVAILABILITY STUDY DESIGN

for

Client – Generic Mfg.

Study Template No. 03

Test Product:	Diltiazem XR
Reference Product:	DILACOR XR® (diltiazem HCl) Extended Release Capsules, RHÔNE-POULENC RORER, COLLEGEVILE, PA
Dosing:	1 x 240 mg
Study Overview:	Randomized, two-way crossover design under fasting conditions
Study Participants:	Young, healthy males (18-45 year old inclusive) N = 32 Confinement: Approximately 10 hours prior to until 36 hours after dose administration.
Screening requirements:	**General:** Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations:** CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation:** Drub abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 16 samples per subject per period Predose (0 hour) and after dosing at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 30, 36 hours.
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing at 3, 5, 7, 9, and 11 hours and as determined by the investigator(s); ECG will be monitored prior to dose administration and after dosing at 4, 6, 8, 10 hours and as determined by the investigator(s).
Analytical Method:	HPLC

CRO

DRAFT BIOAVAILABILITY STUDY DESIGN – REPLICATE DESIGN

for

Client – Generic Mfg.

Study Template No. 04

Test Product:	Warfarin
Reference Product:	COUMADIN® 2 mg Tablet by Dupont Pharma
Dosing:	1 x 2 mg tablets
Study Overview:	Randomized, single-dose, four period crossover replicate design under fasting conditions
Study Participants:	Healthy males & females (18-35 years & 45-65 years old inclusively) N = 36 Confinement: Approximately 10 hours prior to until 24 hours after dose administration. Washout: At least 28 days
Screening requirements:	**General:** Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations:** CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation:** Drug abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 21 samples per subject per period Predose (0 hour) and after dosing at 0.167, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24, 48, 72, 96, 144, 192, 240 hours.
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing as determined by the investigator(s); Blood glucose will be monitored prior to dose administration and after dosing as determined by the investigator(s).
Analytical Method:	HPLC

CRO

DRAFT BIOAVAILABILITY STUDY DESIGN – REPLICATE DESIGN

for

Client – Generic Mfg.

Study Template No. 05

Test Product:	Indapamide
Reference Product:	LOZOL® 2.5 mg Tablets by Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Dosing:	1 x 2.5 mg
Study Overview:	Randomized, single-dose, four period crossover replicate design under fasting conditions
Study Participants:	Healthy males & females (18-35 years & 45-65 years old inclusive) N = 36 Confinement: Approximately 10 hours prior to until 24 hours after dose administration. Washout: At least 7 days
Screening requirements:	**General:** Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations:** CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation:** Drug abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 21 samples per subject per period Predose (0 hour) and after dosing at: 0.167, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 14, 24, 48, 72, 96, 144, 192, 240 hours
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing as determined by the investigator(s); Blood glucose will be monitored prior to dose administration and after dosing as determined by the investigator(s).
Analytical Method:	HPLC

CRO

DRAFT BIOAVAILABILITY STUDY DESIGN – REPLICATE DESIGN

for

Client – Generic Mfg.

Study Template No. 06

Test Product:	Diltiazem XR
Reference Product:	DILACOR XR® (diltiazem HCl) Extended Release Capsules, RHÔNE-POULENC RORER, COLLEGEVILE, PA
Dosing:	1 x 240 mg
Study Overview:	Randomized, four period crossover replicate design under fasting conditions
Study Participants:	Healthy males & females (18-35 years & 45-65 years old inclusively) N = 48 Confinement: Approximately 10 hours prior to until 36 hours after dose administration. Washout Period: At least 7 days
Screening requirements:	**General**: Routine medical history, medication history, physical examination, and electrocardiogram, no history of clinically significant gastrointestinal disease **Screening Evaluations**: CBC with differential, chemistry panel (9), urinalysis, screens for HIV antibody, hepatitis B surface antigen, and drugs of abuse **Check-in Evaluation:** Drug abuse screen **Exit Evaluations:** Physical examination and clinical laboratory measurements which will include CBC with differential & chemistry
Sample Collection:	Blood = 16 samples per subject per period Predose (0 hour) and after dosing at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 30, 36 hours
Subject Safety:	Routine clinical monitoring which includes, blood pressure and heart rate measurements prior to dosing and after dosing at 3, 5, 7, 9, and 11 hours and as determined by the investigator(s); ECG will be monitored prior to dose administration and after dosing at 4, 6, 8, 10 hours and as determined by the investigator(s).
Analytical Method:	HPLC

RESUME

LEON SHARGEL, Ph.D., R.Ph.

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Adjunct Visiting Associate Professor of Pharmacy 1995 - 1996
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HOWARD UNIVERSITY, Washington, DC

Vice President, Scientific Affairs 1995
PHARMAKINETICS LABORATORIES, INC., Baltimore, MD

Director of Biochemistry and Pharmacokinetics 1993 - 1994
FOREST LABORATORIES, INC., New York, NY

Director of Pharmacokinetics 1991- 1993
CHELSEA LABORATORIES, INC., West Hempstead, NY

Associate Professor, Pharmacy and Pharmacology
Director of Pfeiffer Pharmaceutical Sciences Laboratory, Inc., 1982-1991
MASSACHUSETTS COLLEGE OF PHARMACY AND ALLIED HEALTH SCIENCES,
Boston, MA

Section Leader, Pharmaceutics
Associate Professor of Pharmacy and Pharmacology 1975-1982
NORTHEASTERN UNIVERSITY, College of Pharmacy and Allied Health Professions,
Boston, MA

Associate Research Biologist and Group Leader,
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STERLING-WINTHROP RESEARCH INSTITUTE, Rensselaer, NY

Education

Ph.D. Pharmacology, Minors: Physiology, Biochemistry, Drug Metabolism
The George Washington University Medical Center, Washington, DC

B.S. (Cum laude) Pharmacy, University of Maryland, Baltimore, Maryland

Textbooks

Shargel, L. and Yu, A.B.C.
Applied Biopharmaceutics and Pharmacokinetics
Appleton - Lange
East Norwalk, CT

First Edition 1980
Italian Edition 1984
Second Edition 1985
Third Edition 1993
Fourth Editon 1999

Shargel, L.
Editor, *Comprehensive Pharmacy Review*
National Medical Series
Williams & Wilkins, Baltimore, MD

First Edition 1989
Second Edition 1994
Third Edition 1997
First Canadian Edition 1992
Second Canadian Edition 1998
Fourth Edition (in preparation)

Shargel, L.
Associate Editor
Study Guide and Board Review. Pharmacy Practice Exam
National Medical Series
Williams & Wilkins
Baltimore, MD

First Edition 1989
Second Edition 1994
Third Edition 1998

Chapters

Amann AH, Shargel L: "Drug Product Development in the Pharmaceutical Industry," in *Comprehensive Pharmacy Review* , L. Shargel (ed), NMS Series, Williams & Wilkins, Baltimore, Third edition, 1997, Chapter 1.

Shargel L: "Pharmacokinetics," in *Comprehensive Pharmacy Review* , L. Shargel (ed), National Medical Series, Williams & Wilkins, Baltimore, Third edition, 1996, Chapter 6.

Shargel L: "Bioavailability and Bioequivalence," in *Comprehensive Pharmacy Review* , L. Shargel (ed), NMS Series, Williams & Wilkins, Baltimore, Third edition, 1997, Chapter 7.

Yee NS, Shargel L: "Pharmacodynamics," in *Comprehensive Pharmacy Review* , L. Shargel (ed), NMS Series, Williams & Wilkins, Baltimore, Third edition, 1997, Chapter 13.

Shargel L: "Drug Interactions," in *Comprehensive Pharmacy Review* , L. Shargel (ed), NMS Series, Williams & Wilkins, Baltimore, Third edition, 1997, Chapter 20.

Shargel L: "Biopharmaceutics and Pharmacokinetics," in Pharmacy Review, L. Shargel (ed), National Medical Series, Williams & Wilkins, Baltimore, First edition, 1989, Chapter 4., Second edition, 1993, Chapter 6.

Amann AH, Shargel L: "Drug Product Development in the Pharmaceutical Industry," in Pharmacy Review, L. Shargel (ed), National Medical Series, Williams & Wilkins, Baltimore, Second edition, 1993, Chapter 1.

Defelice MJ, Grossman S, Shargel L: "Extemporaneous Prescription Compounding," in Pharmacy Review, L. Shargel (ed), National Medical Series, Williams & Wilkins, Baltimore, Second edition, 1993, Chapter 5.

L. Shargel, "Biopharmaceutics" In: Encyclopedia of Pharmaceutical Technology, J. Swarbrick and J.C. Boylan (Ed), Marcel Dekker, Inc., New York, 1990.

Research Papers

Hurwitz SJ, Coleman NC, Riese N, Loeffler JS, Alexander E, Buswell L, Neben TY, Shargel L, Kramer RK: Distribution of etanidazole into human brain tumors: Implications for treating high grade gliomas, Int J Rad Onc Biol Phys 22:573-576, 1992.

Shargel L, Silverman HI, Cohen P, Brisson J, Dennis S. Bioavailability and cardiovascular safety of Dexatrim^{R} (Phenylpropanolamine Hydrochloride) from a Controlled Release Caplet. Biopharm Drug Dispos 11:569-583 (1990).

Chungi VS, Dittert LW, and Shargel L. Pharmacokinetics of sulfasalazine metabolites in rats following concomitant oral administration of riboflavin. Pharm Res 6: 1067-1072 (1989).

Chungi VS, Rekhi GS, and Shargel L. A simple and rapid liquid chromatographic method for the determination of major metabolites of sulfasalazine in biologic fluids. J Pharm Sci 78: 235-238 (1989).

DiFazio ML, Shargel L: A mathematical utility program to facilitate student comprehension of the pharmacokinetics of the one compartment model. Amer J Pharm Ed 53: 50-53 (1989).

Wiener B, Melby MJ, Faraci PA, Shargel L, Cleveland, RJ: Cefamandole pharmacokinetics during standard and pulsatile cardiopulmonary bypass. J Clin Pharmacol 28: 655-659 (1988).

Figge HS, Figge V, Souney PF, Sacks FM, Shargel L, Kaul AF: Comparison of excretion of nicotinuric acid after ingestion of two controlled release nicotinic acid preparations in man. J Clin Pharmacology 28: 1136-1140 (1988).

DePiero D, Rehki GS, Souney PF, Shargel L: Stability of morphine sulfate solutions frozen in polyvinyl chloride intravenous bags. Pharmacy Practice News pp 1, 39, 40, October (1987).

Yee NS, Shargel L: Effect of cimetidine or ranitidine on hepatic mixed function oxidase activity in the rat. Drug Metab Dispos 14: 580-584, 1986.

Clarke DF, Werbosky OL, Grodin MLL, Shargel L: Conversion from intravenous to sustained release oral theophylline in pediatric patients with asthma. Drug Intel Clin Pharm 20: 700-703, 1986.

Kuttab SH, Nowshed F, Shargel L: Effect of phenobarbital pretreatment on the plasma and urinary levels of l-a-acetylmethadol and its metabolites. J Pharm Sci 74: 331-334 (1985).

Shargel L, Banijamali AR, Kuttab SH: Relationship between azo dye structure and rat azoreductase activity. J Pharm Sci 73: 161-164 (1984).

Ameer B, Divoll M, Abernathy DR, Greenblatt DJ, Shargel L: Absolute and relative bioavailability of oral acetaminophen products. J Pharm Sci 72: 955-958 (1983).

Scheife AH, Grisafe JA, Shargel L: Stability of intravenous nitroglycerin solution. J Pharm Sci 71: 55-59 (1982).

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Ameer B, Greenblatt DJ, Divoll M, Abernathy DR, Shargel L: High pressure liquid chromatographic determination of acetaminophen in plasma: Single dose pharmacokinetic studies. J Chromatog 226: 224-230 (1981).

Shargel L, Stevens JA, Fuchs JE, Yu ABC: Effect of antacid on the bioavailability of theophylline from rapid and timed-release drug products. J Pharm Sci 70: 599-603: (1981).

Baker JJ, Benzinger D, Chalecki BW, Clemans S, Fritz A, O'Melia PE, Shargel L, Edelson J: Disposition of trilostane in the rat and monkey. Arch Int Pharcodyn Therap 243: 4-16 (1980).

Shargel L, Cheung W, Yu ABC: Analysis of antipyrine in plasma samples by high pressure liquid chromatography. J Pharm Sci 68: 1052-1054 (1979).

Clarke RL, Heckeler ML, Gambino AJ, Davor SJ, Harding HR, Pierson AK, Tieger DG, Pearl J, Shargel, LD, Goehl, TJ: (exo, exo)-2-aryltropane-3-carboxylic esters, hypoglycemic agents, with accompanying analgesic activity. J Med Chem 31: 1243-1253 (1978).

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Shargel L, Koss R: Determination of fluorinated hydrocarbon propellants in blood of dogs after aerosol administration. J Pharm Sci 61: 1445-1449 (1972).

MiscellaneousPapers

Milanese, RS, Shargel, L: Covering the cost of prescriptions under Medicare: The case for generic substitution, Health Care Distributor, May, 1999, pp16-17

Abstracts

Shargel L, Amann AH: The dissolution test as a predictor of *in vivo* bioequivalence, Pharm Res 9:S214, 1992.

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Mazel P, Katzen J, Skolnick P, Shargel L. Reduction of sulfoxides in hepatic enzymes. Fed Proc 28: 456 (1969).

Hernandez P, Pittman KA, Shargel L. Stabilization and preservation of hepatic drug metabolizing systems. Pharmacologist 11: 260 (1969).

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Shargel L, Mazel P. Phenobarbital and 3-methylcholanthrene induction of microsomal azoreductase in riboflavin deficient rats. Fed Proc 27: 302 (1968).

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Letters to the Editor

Silverman HI and Shargel L. Phenylpropanolamine Amer Family Physician 34:39-40 (1986).

Shargel, L. Safe Drug? Proper use the key. Pharmacy Times pp 20-21 October (1987).

Classroom and Laboratory Manuals

Shargel L, McGrath MB, Pittman KA. "A Procedural Manual for Routine Assessment of Hepatic Mixed Function Oxidase". Sterling-Winthrop Research Institute, Rensselaer, New York, 1973.

Shargel L, Chryzanowski, FA, Smith PF. "Pharmaceutics Laboratory Manual". Northeastern University Press, 1977, Revised 1979.

Shargel L, Yu ABC. "Applied Biopharmaceutics and Pharmacokinetics". Northeastern University Press, 1978, Revised 1979.

Book Reviews

Shargel L. "The Fate of Drugs in the Organism. A Bibliographic Survey". Vol. 3, by J. Hirtz, Marcel Dekker, in J Med Chem 10: 862 (1977).

Shargel L. "Annual Review of Pharmacology and Toxicology", Vol. 16, H.W. Elliott et al (Ed) Annual Reviews, Inc. in J Med Chem 20 615 (1977).

Shargel L. "A Guide to Vitamins: Their Role in Health and Disease", by J. Marks, University Park Press in Amer J Pharm Ed 41: 147, (1977).

Shargel L. "The Fate of Drugs in the Organism. A Bibliographic Survey", Vol. 4, by J. Hirtz in J Med Chem 20: 1537 (1977).

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Shargel L, Yu ABC. "Drug and Metabolism, Methods and Techniques", Vol. 2, Marcel Dekker in Amer J Pharm Ed 42 (1978).

Shargel L. "Drug Level Monitoring. Analytical Techniques, Metabolism and Pharmacokinetics", W. Sadee and G.C.M. Beeler, Wiley, New York, 1980 in J Med Chem 23: 1271 (1980).

Shargel L. "Extrahepatic Metabolism of Drugs and Other Foreign Compounds", T.E. Gram (Ed) Spectrum, New York 1980 Amer J Pharm Ed 45: 223 (1981).

Shargel L. "Basic Clinical Pharmacokinetics", M.E. Winter, Applied Pharmaceutics Inc., San Francisco, 1980 in Pharmaceutical Technology (1982).

Shargel L, Breen PJ. "Graphic Approach to Clinical Pharmacokinetic", Drug Intelligence Publications, 1983 in Amer J Pharm Ed 48: 456 (1984).

Shargel L. "Bioactivation of Foreign Compounds", M.W. Anders (Ed) Academic Press, New York, 1985 in J Med Chem 29: 592 (1986).

Shargel L, Breen PJ. "Drug Fate and Metabolism. Methods and Techniques", E.R. Garrett, J.L. Hirtz (Ed) Marcel Dekker, New York, 1985 in J Med Chem 29: 1555-1556 (1986).

Shargel L. "Dictionary of Pharmacy", J.H. Fincher, University of South Carolina Press. in Amer J Pharm Ed 51: 107 (1987).

Shargel L. "Pharmacokinetics: Regulatory, Industrial, Academic Perspectives", P.G. Welling; F.L.S. Tse (Ed), Marcel Dekker, New York, 1988, in J Pharm Sci ,1990.

ORAL PRESENTATIONS

"Analysis of Drugs in Biological Tissue" Presented before the Boston Bacteriological Club, February 25, 1976.

"Are All Drugs Created Equal?" A discussion of bioavailability and bioequivalence of drug products. Presented to the U.S. Naval Research Company 1-1, March 29, 1976.

"Career Opportunities Discussion" Presented to SAPhA and Rho Chi Meeting, May 3, 1976.

Research Seminar presented to the Department of Medicinal Chemistry and Pharmacology Colloquia, May 10, 1976.

"Problems of Human Drug Research" Presented before the Boston Association of Retail Druggists, July 17, 1976.

"Inhibition of Hepatic Microsomal Enzymes by Chloramphenicol", J.P.E.T., 203:338 (1977). Presented before the Pharmacology Journal Club, April, 1977.

"Toxicity of Fluorinated Hydrocarbons (Freons)" Presented to the Naval Reserve, NR VTU Research 0103, Boston, MA, June, 1977.

"Brand Name vs. Generic Name Drug/Does Price Make the Difference?" Presented to the Boston Association of Retail Druggists, July, 1978.

"Where this College should be in 1984" Retreat, College of Pharmacy and Allied Health Professions, Northeastern University, September, 1978.

"Interdisciplinary Research" Retreat, College of Pharmacy and Allied Health Professions, Northeastern University, December, 1978.

"Problems of Human Studies" Seminar, Pharmacology Section Northeastern University, June, 1979.

"Product Selection on Bioavailability" Maine Pharmaceutical Association Meeting, September, 1979 (sponsored by the Upjohn Company).

"Considerations in Human Drug Research" Presented to the Northeastern University Health Care Faculty, Northeastern University, April, 1980.

"Bioavailability and Biopharmaceutics" Continuing Education Program on Drug Product selection, Northeastern University, June, 1980.

"Bridging the Gap Between Basic Sciences and Clinical Practice: Teaching, Research and Service" Opportunities in Pharmaceutics". NABP/AACP District I Annual Meeting, Providence, Rhode Island, October, 1980.

"Drug Interaction for the Health Practitioner" Continuing Education Program Northeastern University, November, 1980.

"Therapeutic Drug Monitoring" Guest Lectures for Advanced Clinical Chemistry Course, Northeastern University, December, 1981-1983.

"Pharmacokinetic Principles in Clinical Medicine" Veteran's Administration Hospital, Boston, MA, February, 1982.

"Effect of Antacid on Theophylline Pharmacokinetics" Presented to the Department of Pharmacology and Experimental Therapeutics, Boston, University Medical Center, March, 1983.

"Biopharmaceutic/Pharmacokinetic Study Procedures and Laboratory Practices" Associates of Clinical Pharmacology, Annual Meeting, Boston, October 1984.

"Effect of Cimetidine or Ranitidine on Hepatic Mixed Function Oxidase Activity in the Rat" Presented to the School of Pharmacy, University of Connecticut, March, 1986.

"The FDA's Orange Book Coding System" Continuing Education Seminar, North Carolina Mutual Wholesale Company, Durham, NC, October, 1991

Breen PJ, Jambhekar S, Shargel L. "Relationship of Drug Protein Binding Constants Derived from the Scatchard Equation to the Fraction of Drug Bound", Society of Toxicology, New England Chapter, Cambridge, MA, June, 1985.

DeFelice M, Shargel L, "Pharmacy Prescription Survey", American Association of Colleges of Pharmacy (AACP/NAPB), District I, September, 1985, Burlington, VT.

Shargel L: Toxicokinetics - Practical Applications of Pharmacokinetics, Chemical Carcinogenesis Branch, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC, April, 1991

Shargel, L: Strategies and Problems in the Development of Generic Drug Products, Fourth Phoenix International Symposium, Montreal, Canada. May, 1993

Shargel, L: Pharmacokinetics of Hydromorphone (Dilaudid), National Institutes of Drug Abuse, Division of Intramural Research, Baltimore, MD, September, 1996.

Shargel, L: Economic Impact of Current Legislative and Regulatory Issues on the Generic Drug Industry: Overview of Issues, presented at the NAPM Workshop on Current Regulatory and Legislative Issues for API Manufacturers, New York, NY, March, 1998

Shargel, L: Generic Drug Substituion and Narrow Therapeutic Index Drugs, NAPM Mid-Year Meeting and Educational Conference, Washington, D.C., June, 1998

Shargel, L: Scientific, Regulatory and Legislative Aspects of Generic Pharmaceutical Development and Sale, The National Congress on the Futrure of Pharmaceuticals in Medicare. Innovation and Cost Management, Arlington, VA, December 9, 1999.

RELATED PROFESSIONAL ACTIVITIES

PMA Coordinated Industry Program for Pharmacy Faculty
Visitation to Endo Laboratories, Inc., Subsidiary of I.E. duPont de Nemours and Co., Inc., 1980.

Visiting Scientist for Minority Institutions (Sponsored by NIGMS, National Institutes of Health, 1982-1991.

National Institutes of Health Special Study Section for Grant Reviews, 1982.

National Institute of Environmental Health Sciences Special Study Section for Grant Reviews, Bioanalytical Chemistry Support, 1991

Member, Controlled Substances Advisory Board, The Commonwealth of Massachusetts, Department of Public Health, 1982-1984.

Member, Drug Formulary Commission, Commonwealth of Massachusetts, 1987 - 1991 (Member, Subcommittee for Public Comment)

Reviewer, Chapter 19, "Weight Control Products" in Handbook of Nonprescription Drugs, 9th edition, American Pharmaceutical Association, Washington, DC, 1990, 1993

Organizer and Founder, "Graduate Research Day" Annual event at MCP/AHS, 1983-1990.

Advisor, Chinese Student Organization, MCP/AHS, 1985-1991.

PMA Pharmaceutical Industry Visiting Scientist
University of Minnesota, College of Pharmacy, January, 1992
University of Kentucky, College of Pharmacy, April, 1993

External Examiner, Rhodes University, Grahamstown, South Africa, February, 1992

Registered Pharmacist, District of Columbia, Massachusetts, Maryland

Charter Member, American Association of Pharmaceutical Sciences, Member, 1994 -, Co-Chair, 1997, Chair, 1998 - 1999 - Pharmacokinetics, Pharmacodynamics and Drug Metabolism (PPDM) Section, Eastern Regional Meeting; Program Chair, Eastern Regional Meeting, June, 2000

Member, Institutional Review Board (IRB), National Institutes of Health, National Institute on Drug Abuse, Division of Intramural Research, Baltimore, MD, 1996 - 1997

Moderator: Pharmaceutical Equivalents of Biological Drugs: Regulatory/Scientific Hurdles and Policy Issues, NAPM Annual Meeting and Educational Conference, Rio Grande, PR, Februrary, 1998

Moderator, Drug Abuse, AAPS Eastern Regional Meeting, Parsippany, NJ, June, 1998

Moderator: Generic Drug Substituion and Narrow Therapeutic Index Drugs, NAPM Mid-Mid-Year Meeting and Educational Conference, Washington, D.C., June, 1998

Moderator, Bioequivalence Issues, Generic Trade Associations/FDA Fall Technical Workshop, The Generic Pharmaceutical Industry: Regulatory and Scientific Challenges," Bethesda, MD, November, 1998

Moderator: Generic Drug Substitution Issues, NAPM Mid-Mid-Year Meeting and Educational Conference, Newark, NJ, May, 1999

Moderator: PPDM Symposium: Bioavailability/Bioequivalence Issues, Eastern Regional Meeting, American Association of Pharmaceutical Scientists, Parsippany, NJ, June, 1999

Graduate Student Advisor[1]

Ph.D. Dissertations

Ramachandra R. Thirucote, Ph.D.
Development and Characterization of a Transdermal Drug Delivery System Utilizing an Ultraviolet Curing Polymer Matrix, Massachussetts College of Pharmacy & Allied Health Sciences, 1992

Vinod S. Chungi, Ph.D.
The Effect of Riboflavin on the Pharmacokinetics of AZO Compounds in the Rat, Massachussetts College of Pharmacy & Allied Health Sciences, 1988

Philip J. Breen, Ph.D.
Effect of Azathioprine and 6-Mercaptopurine on Hepatic Metabolism in Rats: In vivo/In vitro Correlation, Massachussetts College of Pharmacy & Allied Health Sciences, 1987

Sompong Panichpol, Ph.D.
A Study of the Effect of Dimethyl Sulfoxide on Phenylbutazone Pharmacokinetics in Rabbits, Massachussetts College of Pharmacy & Allied Health Sciences, 1983

M.S. Theses

Patricia A. Lilagan, M.S.
Biopharmaceutics and Pharmacokinetics of a Novel Controlled Release Dosage Form of Acetaminophen, Massachussetts College of Pharmacy & Allied Health Sciences, 1991

Laura Labarquilla, M.S.
Freeze-Drying of Emulsions in the Presence of Cryoprotectants, Massachussetts College of Pharmacy & Allied Health Sciences, 1990

Ming-Chia Huang, M.S.
Dissolution and Bioavailability of Nicotinic Acid from Controlled Release Dosage Forms, Massachussetts College of Pharmacy & Allied Health Sciences, 1987

Manju Biswas, M.S.
A Study of the Effect of Nicotinic Acid on Hepatic Mixed Function Oxidase in Rats, Massachussetts College of Pharmacy & Allied Health Sciences, 1987

Tsong-Mei Tsai, M.S.
Effect of Oxandrolone on the Elimination of Theophylline, Massachussetts College of Pharmacy & Allied Health Sciences, 1983

Jerry Masnyj, M.S.
Effect of Stannous Fluoride on Hepatic Mixed Function Oxidase Activities in Rats, College of Pharmacy & Allied Health Professions, Northeastern University, 1981

Andrea H. Scheife, M.S.
Stability of Intravenous Nitroglycerin, College of Pharmacy & Allied Health Professions, Northeastern University, 1981

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[1]Only those students for whom I was the major professor are listed.