SRI LAKSHMI NARAYANA INSTITUTE OF MEDICAL SCIENCES

Osudu, Agaram Village, Kottakuppam post, Puducherry - 605502

Date: 17.01.2018

From
Dr.G.Somasundaram
Professor and Head,
Department of Pharmacology
Sri Lakshmi Narayana Institute of Medical sciences
Pondicherry

To
The Dean,
Sri Lakshmi Narayana Institute of Medical sciences
Pondicherry

Sub: Permission to conduct value-added course:Therapeutic window phenomena

Dear Sir,

With reference to the subject mentioned above, the department proposes to conduct a value-added course titled:**Therapeutic window phenomena** February to August 2018. We solicit your kind permission for the same.

Kind Regards

Dr.G Somasundaram

FOR THE USE OF DEANS OFFICE

Names of Committee members for evaluating the course:
Dean: Dr.Sugumaran HOD:Dr.G.Somasundaram Expert: Dr.Jaikumar.S Dr.Jaynsheela.J
The committee has discussed about the course and is approved.

Dean Subject Expert HOD

OFFICE OF THE DEAN

Sri Lakshmi Narayana Institute of Medical Sciences

OSUDU, AGARAM VILLAGE, VILLIANUR COMMUNE, KUDAPAKKAM POST,
PUDUCHERRY - 605 502

[Recognised by Medical Council of India, Ministry of Health letter No. U/12012/243/2006-ME (P -II) dt. 1/07/2011]
[Affiliated to Bharath University, Chennai - TN]

Circular **Date:** 18.01.2018

Sub: Organising Value-added Course: Therapeutic Window Phenomena

With reference to the above mentioned subject, it is to bring to your notice that Sri Lakshmi Narayana Institute of Medical Sciences is organizing "**Therapeutic Window Phenomena**" **February to August 2018**. The course content is enclosed below."

The application must reach the institution along with all the necessary documents as mentioned. The hard copy of the application should be sent to the institution by registered/ speed post only so as to reach on or before **January 31st 2018** Applications received after the mentioned date shall not be entertained under any circumstances.

Dean

Encl: Copy of Course content

Annexure 2 – Course Proposal

Course Title: Therapeutic window phenomena
Course Objective

1. Introduction
2. Purpose Of Therapeutic Drug Monitoring
3. Measuring Plasma Drug Concentration In Therapeutic Drug Monitoring
4. Analytical Issues In Therapeutic Drug Monitoring
5. Practical Issues In Therapeutic Drug Monitoring
6. Pharmacoeconomic Impact Of Therapeutic Drug Monitoring
7. Pharmacogenetics and TDM
8. Role of clinician in TDM
9. Recognize clinical areas where implementation of TDM may have a positive impact on patient care

Course Outcome: TDM plays an important role in the development of safe and effective therapeutic medications and individualization of these medications.Additionally, TDM can help to identify problems with medication compliance among noncompliant patient cases

Course Audience: 2nd Year MBBS Students

Course Coordinator: Dr.G.Somasundaram,

Course Faculties with Qualification and Designation: Dr.S.Jaikumar
Asst.Prof.Dept of Pharmacology
Dr.J.Jayasheela
Asst.Prof.Dept of Pharmacology

Course Curriculum/Topics with schedule (Min of 30 hours)

S No	Date	Topic	Time	Hours
1	13.02.2018	Introduction	4-7 pm	3
2	20.02.2018	Purpose Of Therapeutic Drug Monitoring	4-7 pm	3
3	13.03.2018	Measuring Plasma Drug Concentration In Therapeutic Drug Monitoring	4-7 pm	3
4	20.03.2018	Analytical Issues In Therapeutic Drug Monitoring	4-7 pm	3
5	10.04.2018	Practical Issues In Therapeutic Drug Monitoring	4-7 pm	3
6	15.05.2018	Pharmacoeconomic Impact Of Therapeutic Drug Monitoring	4-7 pm	3
7	12.06.2018	Pharmacogenetics and TDM	3-7 pm	3
8	10.07.2018	Role of clinician in TDM	3-7 pm	3
9	07.08.2018	Recognize clinical areas where implementation of TDM may have a positive impact on patient care	3-7 pm	3
			Total Hours	30

Dasgupta, Amitava, PhD

Dasgupta, Amitava, PhD.

VALUE ADDED COURSE

1. Name of the programme & Code

THERAPEUTIC WINDOW PHENOMENA

2. Duration & Period

February to August 2018

3. Information Brochure and Course Content of Value Added Courses

Enclosed as Annexure- I

4. List of students enrolled

Enclosed as Annexure- II

5. Assessment procedures:

Short answers *Enclosed as Annexure- III*

6. Certificate model

Enclosed as Annexure- IV

7.No. of times offered during the same year:

February August 2018

8. Year of discontinuation: 2018

9. Summary report of each program year-wise

Value Added Course- February August 2018

Sl. No	Course Code	Course Name	Resource Persons	Target Students	Strength & Year
1	PH06	Therapeutic Window Phenomena	Dr.S.Jaikumar Dr.J.Jayasheela	2nd MBBS	20 (Feb-Aug-18)

10. Course Feed Back

Enclosed as Annexure- V

RESOURCE PERSON **COORDINATOR**

Therapeutic Window phenomena

Particulars	Description
Course Title	Therapeutic window phenomena
Course Code	PH06
Objective	1. Introduction 2. Purpose Of Therapeutic Drug Monitoring 3. Measuring Plasma Drug Concentration In Therapeutic Drug Monitoring 4. Analytical Issues In Therapeutic Drug Monitoring 5. Practical Issues In Therapeutic Drug Monitoring 6. Pharmacoeconomic Impact Of Therapeutic Drug Monitoring 7. Pharmacogenetics and TDM 8. Role of clinician in TDM 9. Recognize clinical areas where implementation of TDM may have a positive impact on patient care
Further learning opportunities	TDM plays an important role in the development of safe and effective therapeutic medications and individualization of these medications. Additionally, TDM can help to identify problems with medication compliance among noncompliant patient cases
Key Competencies	On successful completion of the course the students will have skill to interpret the values in therapeutic drug monitoring
Target Student	II MBBS Students
Duration	30hrs Every Feb to Aug 2016
Theory Session	10hrs
Practical Session	20hrs
Assessment Procedure	MCQ

INTRODUCTION

Therapeutic drug monitoring (TDM) is generally defined as the clinical laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures. Otherwise, TDM refers to the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window . By combining knowledge of pharmaceutics, pharmacokinetics, and pharmacodynamics, TDM enables the assessment of the efficacy and safety of a particular medication in a variety of clinical settings. The goal of this process is to individualize therapeutic regimens for optimal patient benefit. Traditionally, TDM involves measuring drug concentrations in various biological fluids and interpreting these concentrations in terms of relevant clinical parameters. Clinical pharmacists and pharmacologists use pharmacokinetic principles to assess these interpretations. The science of TDM introduced a new aspect of clinical practice in the 1960s with the

publication of initial pharmacokinetic studies linking mathematical theories to patient outcomes From there, clinical pharmacokinetics emerged as a discipline in the late 1960s and early 1970s. Pioneers of drug monitoring in the 1970s focused on adverse drug reactions and demonstrated clearly that by constructing therapeutic ranges, the incidence of toxicity to drugs such as digoxin phenytoin, lithium, and theophylline could be reduced. The emergence of clinical pharmacokinetic monitoring was encouraged by the increasing awareness of drug concentration-response relationships, the mapping of drug pharmacokinetic characteristics, the advent of high-throughput computerization, and advancements in analytical technology . The more recent explosion of pharmacogenetic and pharmacogenomic research has been fuelled by the tremendous amount of genetic data generated by the Human Genome Project (HGP). In 1990, the HGP began its quest to map the complete set of genetic instructions of the human genome consisting of approximately 3.2 billion base pairs encoding up to 100,000 genes located on 23 pairs of chromosomes Although originally conceived as a 15-yr project, the HGP was essentially completed by 2001. Recent advancements in gene chip technology have ushered in a new era of gene based medicinal and drug therapies.

PURPOSE OF THERAPEUTIC DRUG MONITORING

Performing TDM requires a multidisciplinary approach Accurate and clinically meaningful drug concentrations are attainable only by complete collaboration by a TDM team, typically comprised of scientists, clinicians, nurses, and pharmacists. Excellent communication among team members is necessary to ensure that best practices in TDM are achieved

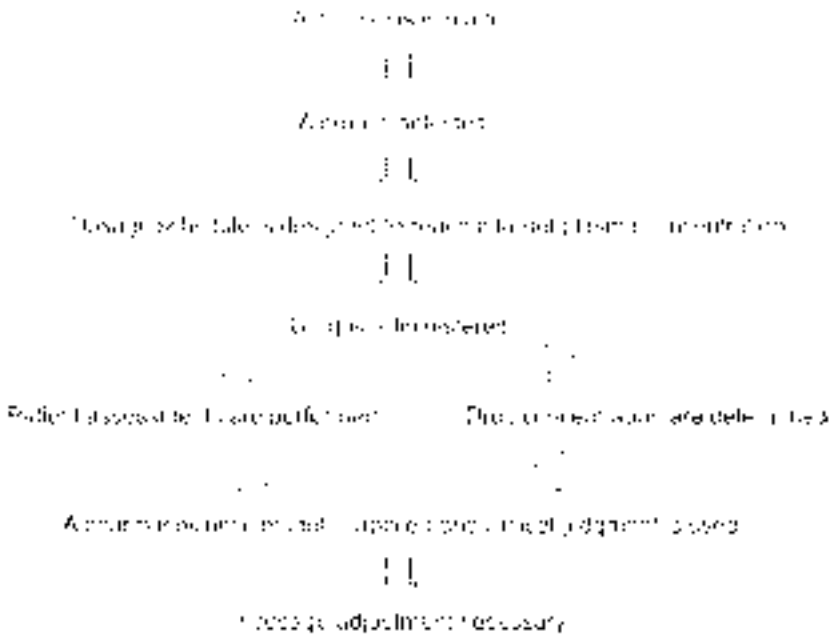


Figure 1

Process for monitoring drug therapy

The indications for drug monitoring have widened to include efficacy, compliance, drug drug interactions, toxicity avoidance, and therapy cessation monitoring (Table 1). Plasma drug concentration measurements alone may be helpful in several circumstances, although each indication may not apply equally to every drug Measuring plasma concentrations may be helpful, however, as a low measurement reflects either poor recent compliance or under treatment. Poor compliance is implicated if the patient is prescribed a dose that is unlikely to be associated with a measured low concentration or if a previous measurement suggested that the plasma concentration should be higher for the given dose. When initiating drug therapy, the physician may find it useful to measure the plasma drug concentration and tailor the dosage to the individual. This directive applies to all drugs, although it is most important for those with narrow therapeutic ranges such as lithium, cyclosporine, and aminoglycoside antibiotics.

Table 1

Indications for requesting plasma drug concentrations

Monitoring compliance
Individualizing therapy
during early therapy
during dosage changes
Diagnosing undertreatment
Avoiding toxicity
Monitoring and detecting drug interactions
Guiding withdrawal of therapy

If the dosage regimen must be altered for any reason at a later stage of treatment, for example, in patients with renal failure, measuring plasma concentrations again may be helpful. Undertreatment of an established condition may be concluded if a poor clinical response is observed. However, when the drug is being used as prophylaxis, it is impossible to monitor a response. Thus, the physician can select a dosage that will produce a certain target plasma concentration. This dictum applies particularly to lithium in preventing manic-depressive attacks, to phenytoin in preventing fits after neurosurgery or trauma, and to cyclosporine in preventing transplant rejection. In all cases, plasma concentration measurements obtained and scrutinized during the early treatment stages enable the physician to avoid toxic plasma concentrations. In many cases, drug toxicity can be diagnosed clinically. For example, it is relatively easy to recognize acute phenytoin toxicity, and measuring the plasma concentration may not be necessary for diagnosis, although it may be helpful in adjusting the dosage subsequently. On the other hand, digoxin toxicity may mimic certain symptoms of heart disease, and measuring the

plasma concentration in cases in which toxicity is suspected may be helpful in confirming the diagnosis. In a study by Aronson and Hardman measurement of the plasma digoxin concentration in 200 patients treated with digitalis lanata preparations (digoxin, lanatoside C, betamethyl-digoxin) enabled the monitoring of certain outcomes that would not be apparent otherwise. Notably, the important overlap between "toxic" and "nontoxic" plasma concentration values limits use of the method in the diagnosis of digitalis toxicity (Fig. 2). However, in digitalis-treated patients with toxicity associated with digitalis plasma concentrations under 2.0 ng/mL, the method can detect digitalis sen-sitivity. Aronson and Hardman determined that a dosage selection based on plasma drug concentration assessment led to a decrease of digitalis toxicity to below 4%. This method is not yet widely available. Thus, it should be noted that plasma digoxin concentration measurements should be obtained and evaluated in digitalis treated patients with borderline renal function, in aged subjects, and in patients with rapid atrial fibrillation who require higher digitalis doses for heart rate control (Fig. 3).

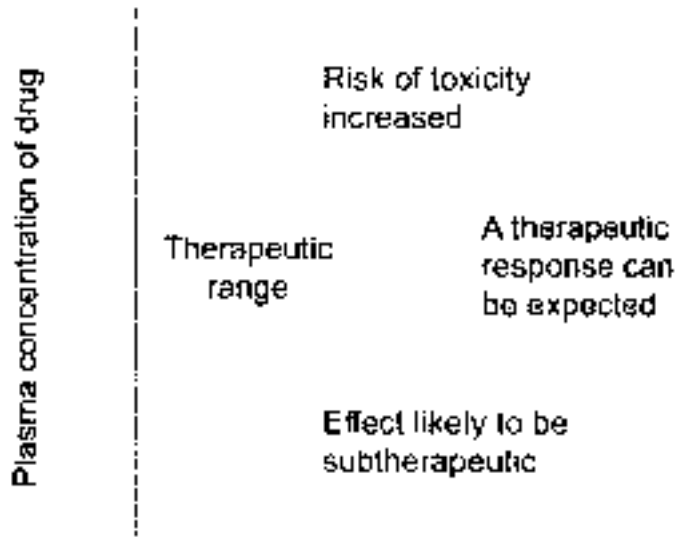
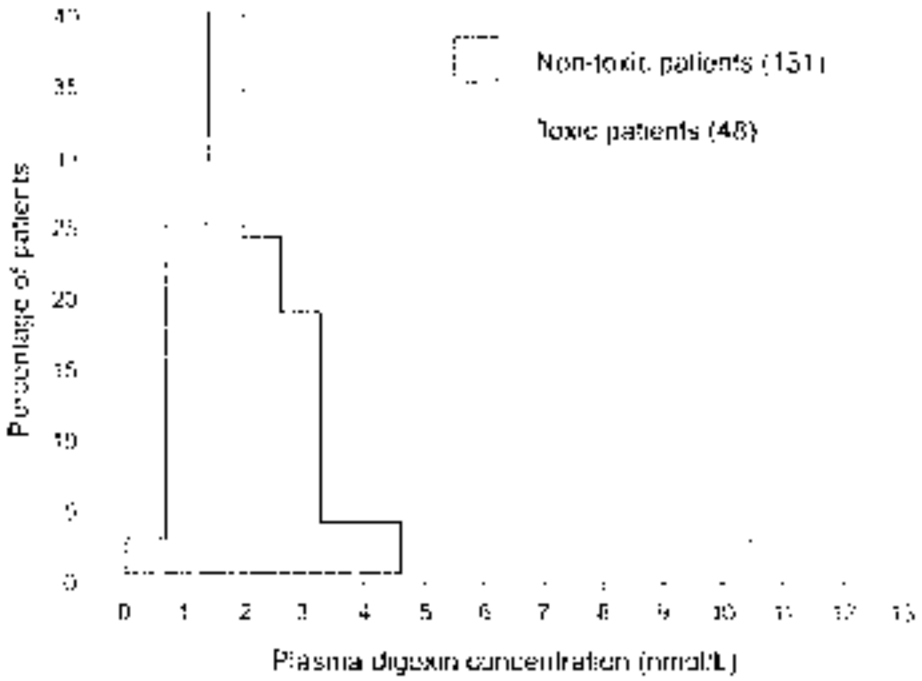


Figure 2

[illegible] [20].



MEASURING PLASMA DRUG CONCENTRATION IN THERAPEUTIC DRUG MONITORING

The contribution of pharmacokinetic variability to differences in dose requirements can be identified by measuring the drug concentration at steady state and modifying the dose to attain a

desired concentration known to be associated with efficacy. However, there is substantial inter-individual pharmacodynamic variability at a given plasma concentration hence a range of concentrations rather than a single level is usually targeted. For a limited number of drugs for which there is a better relationship between plasma or blood concentration-response than dose-response, the measurement of plasma or blood concentrations has become a valuable surrogate index of drug exposure in the body

Pressures continue within the health care system to provide services at the lowest possible cost. Thus, the role of many drug assay laboratories is to measure the concentration of a therapeutic drug in a blood sample and relate this number to a therapeutic range published in the literature. Therapeutic drug measuring is only one part of TDM that provides expert clinical interpretation of drug concentration as well as evaluation based on pharmacokinetic principles. Expert interpretation of a drug concentration measurement is essential to ensure full clinical benefit. Clinicians routinely monitor drug pharmacodynamics by directly measuring the physiological indices of therapeutic responses, such as lipid concentrations, blood glucose, blood pressure, and clotting. For many drugs, either no measure of effect is readily available, or the method is insufficiently sensitive Therefore, the process of TDM is predicted on the assumption that a definable relationship exists between dose and plasma or blood drug concentration, and between the blood drug concentration and pharmacodynamic effects . Measuring the plasma drug concentration may guide clinicians to stop treatment under two known circumstances. First, treatment should cease if the plasma digoxin concentration is below the therapeutic range in a patient whose clinical condition is satisfactory so that digoxin withdrawal is unlikely to lead to clinical deterioration. Note that this use of the plasma concentration measurement depends on the concept that there is a lower end to the therapeutic range. This is not true for other drugs,

particularly phenytoin. If there is no response to lithium and the serum concentration is at the upper end of the therapeutic range, then increased dosage is unlikely to be beneficial, and the risk of toxicity is high. Withdrawal of lithium and the use of a different treatment would be justified. Drug concentration measurements are requested to assist the management of a patient's current medication regimen or to screen for a medicine. Procedures may also be implemented to assess whether requests for drug assays are warranted before the assays are actually performed, thereby ensuring the rational utilization of resources. This is often time consuming for senior personnel, but can be cost-effective as it may prevent expensive tests that do not assist either immediate or long term patient management.

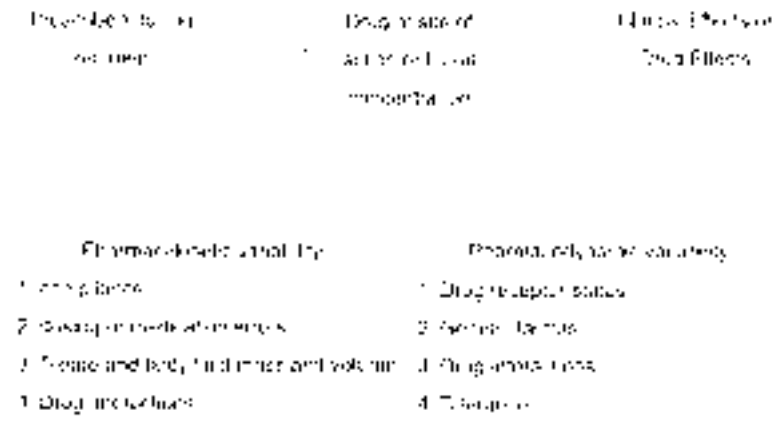


Figure 1

Schematic representation of pharmacokinetic and pharmacodynamic factors that affect pharmacokinetic and pharmacodynamic drug profiles

For a small number of drugs, measuring the plasma concentration is helpful in clinical practice. Table 2 presents the criteria that must be satisfied for the drug plasma concentration to be useful

Table 2

Criteria that a drug should satisfy for plasma concentration measurements to be useful

Difficulty in interpreting clinical evidence of therapeutic or toxic effects
A good relationship between the plasma drug concentration and the therapeutic or toxic effect, or both
A low toxic: therapeutic ratio
Dose does not metabolize to important active metabolites

Even for drugs that fulfill these criteria, some controversy exists about the usefulness of monitoring their plasma concentrations First, it has been argued that no good evidence demonstrates that targeting plasma concentrations improves the therapeutic outcome and that the therapeutic value of plasma monitoring must be tested .However, these arguments ignore the underlying principle: a stronger relationship exists between plasma concentration and effect than between dose and effect suggesting that it should be possible to improve therapy with a drug by monitoring its plasma concentrations. Second, it is argued that the value of the technique is reduced by problems in defining therapeutic ranges, such as those encountered when conditions alter a drug's pharmacodynamic effects However this argument merely emphasizes the need for proper interpretation of plasma drug concentrations under such conditions. Third, some argue that the plasma concentration itself is being treated rather than the patients, and that monitoring is rendered useless by, for example, an inappropriate timing of sampling. We argue that this last point indicates that the information provided by plasma drug concentration monitoring is being misused . There is no justification for routine measurements of plasma drug concentrations

without a definite purpose. Indeed, routine measurement of the plasma drug concentration without a clear purpose is as irresponsible as obtaining no measurement at all.

SUMMARY

The use of TDM requires a combined approach encompassing pharmaceutical, pharmacokinetic, and pharmacodynamic techniques and analyses. The appropriate use of TDM requires more than a simple measurement of patient blood drug concentration and a comparison to a target range. Rather, TDM plays an important role in the development of safe and effective therapeutic medications and individualization of these medications. Additionally, TDM can help to identify problems with medication compliance among noncompliant patient cases. When interpreting drug concentration measurements, factors that need to be considered include the sampling time in relation to the dose, the dosage history, the patient's response, and the desired clinical targets. This information can be used to identify the most appropriate dosage regimen to achieve the optimal response with minimal toxicity.

VALUE ADDED COURSE

Annexure II

SRI LAKSHMI NARAYANA INSTITUTE OF MEDICAL SCIENCES

Participant list of Value added course: Therapeutic window phenomena Feb to AUG 2018

Sl. No	Name of the Student	Register No	Signature
1	PRIYANKA BANDOPADHYAY	U17MB351	Priyanka
2	PRIYANKA KUMARI	U17MB352	Priyanka
3	PRIYANKA SINGH	U17MB353	
4	RAAGAVI.S	U17MB354	
5	RAHUL RAI	U17MB355	
6	RICHI SWARN	U17MB356	
7	RINI DAS	U17MB357	Rini das
8	RISHABH SUMAN	U17MB358	
9	RISHIKA	U17MB359	
10	RISHIRAJ KAR	U17MB360	
11	RIYA M.A	U17MB361	
12	ROHIQUL ISLAM	U17MB362	
13	ROHAN DAS	U17MB363	
14	SAKSHI SHARMA	U17MB364	
15	SAMYUKTHA	U17MB365	
16	SANORITA	U17MB366	
17	SANTOSHKUMAR NK	U17MB367	
18	SAPTARSHI CHATTOPADHYAY	U17MB368	
19	SATHYA JAINAUB T.S.	U17MB369	
20	SHABAN OS	U17MB370	

PROFESSOR & HOD
DEPARTMENT OF PHARMACOLOGY
Sri Lakshmi Narayana Institute of Medical Sciences
PUDUCHERRY - 605 502

Annexure - III

THERAPEUTIC WINDOW PHENOMENA

MCQ

Course Code: PH 06

1. The time period that must elapse between the time of administration of a drug and the time that a serum level can be drawn depends on which of the following pharmacokinetic parameters of that drug? A. Elimination half-life

B. Distribution half-life

C. Clearance

D. Steady-state serum concentration

2. A drug that causes hepatic enzyme induction and increases the metabolism of other drugs is

A. phenobarbital.

B. digoxin.

C. theophylline.

D. lithium

3. A change in the dosing regimen of a patient receiving phenobarbital is made. Phenobarbital has a half-life of 90 hours. The patient receives a dose every 12 hours. To verify that the new dose is appropriate, a sample should be drawn and tested

A. the next morning.

B. after 5 doses have been given.

C. in 4 to 5 days.

D. in about 15 days

4. Serum drug assays typically measure

A. total drug (both protein-bound drug and unbound drug).

B. unbound drug only.

C. protein-bound drug only.

D. volume of distribution

5. A patient has a phenytoin concentration of 15 ug/mL. Upon calling the physician with this result, the technologist is informed that the patient appears toxic. Given the nature of phenytoin, which of the following steps will most readily indicate that a total concentration of 15 ug/mL is consistent with toxicity and therefore an analytically correct value?

A. Recheck the analytical run to ensure that all quality control is correct.

B. Recheck the result by rerunning a fresh sample from the original collection tube.

C. Request a fresh sample from the patient.

D. Check to see if the patient has a decreased albumin concentration

6. When a drug is being administered on a repeating pattern, steady-state serum drug concentrations are achieved after approximately how many drug half-lives have elapsed?

A. One

B. Two

C. Five

D. The number varies with the drug.

7. Ultrafiltration is clinically useful when used for the following:

A. Removal of DLIF and measurement of free phenytoin, free valproic acid, and free digoxin in the presence of Digibind

B. Measurement of free phenytoin, free valproic acid, and free digoxin in the presence of digibind

C. Measurement of free phenytoin and free valproic acid

D. Measurement of free digoxin in the presence of digibind and removal of DLIF

8. Factors that can affect the results of therapeutic drug monitoring include

A. interactions between drugs.

B. accurate documentation of draw times.

C. drug metabolism and elimination.

D. All of the above

9. Which of the following drugs have long distribution phases so that samples must be drawn 6 to 12 hours after a dose?

A. Cyclosporine, carbamazepine

B. Lithium, digoxin

C. Phenytoin, phenobarbital

D. Procainamide, primidone

10. The initial peak serum drug concentration achieved after a drug is administrated by intravenous bolus is influenced most by which pharmacokinetic parameter?

A. Clearance

B. Elimination half-life

C. Steady-state serum concentration

D. Volume of distribution

Student Feedback Form

Course Name: Therapeutic window phenomena

Subject Code: **PH 06**

Name of Student: [illegible] Roll No.: [illegible]

We are constantly looking to improve our classes and deliver the best training to you. Your evaluations, comments and suggestions will help us to improve our performance

Sl. NO	Particulars	1	2	3	4	5
1	Objective of the course is clear				✓	
2	Course contents met with your expectations					✓
3	Lecturer sequence was well planned					✓
4	Lectures were clear and easy to understand				✓	
5	Teaching aids were effective				✓	
6	Instructors encourage interaction and were helpful					✓
7	The level of the course				✓	
8	Overall rating of the course	1	2	3	4 ✓	5

** Rating: 5 – Outstanding; 4 - Excellent; 3 – Good; 2– Satisfactory; 1 Not-Satisfactory*

Suggestions if any:

Date: 09.08.2018

From
G.Semgunadaran.
Department Of Pharmacology.
Sri Lakshmi Narayana Institute ofMedical Sciences
Bharath Institute of Higher Education and Research.
Chennai.

Through Proper Channel

To
The Dean.
Sri Lakshmi Narayana Institute ofMedical Sciences
Bharath Institute of Higher Education and Research.
Chennai

Sub: Completion of value-added course: Therapeutic Window Phenomena

Dear Sir,

With reference to the subject mentioned above, the department has conducted thevalue-added course titled, **Therapeutic Window Phenomena** on **Feb to Aug 2018**. We solicit your kind action to send certificates for the participants, which is attached with this letter. Also, I am attaching the photographs captured during the conduct of the course.

Kind Regards

G.Semgunadaran

Encl: Certificates

Photographs