let us move to the second phase of our

and uh introduce you to the basic

concepts in pharmacokinetics and its

clinical applications

we will talk uh about the apparent

volume of distribution and the clearance

parameters these are two parameters that

we call primary pharmacokinetic

parameters then we will address first

order kinetics the vast majority of

drugs that we use in clinical medicine

follow the pattern of first order

kinetics of drug elimination but there

are exceptions and that would lead us to

discuss

Michaelis mental kinetics for drug

elimination

so pharmacokinetics the quantitative

analysis of the time course of drug

absorption

drug distribution

drug metabolism and excretion or

elimination from the body

schematically here

we prescribe a dose or administer a dose

of medication to a human subject

then we need to wait for the process of

absorption to take place so that the

drug can be carried typically from the

gastrointestinal tract to the systemic

circulation the drug in plasma May

circulate as the free drug but also May

bind to plasma proteins like albumin and

and again you have this reversible

equilibrium between drug that is free in

plasma and drug that is protein bound

the extent of protein binding varies

tremendously depending on the drug in

question

then drug elimination will take place

but of course drug distribution from the

plasma compartment

will take place

the drug may actually distribute to most

tissues and you may find uh nonspecific

binding of drugs to tissues but what

were really interested is in the

distribution of the drug to its site of

pharmacological action what we call the

biophase and of course the study of

receptor binding and ultimately the

effect of the drug that were looking

for

now again uh drug metabolism May

contribute to elimination and renal

excretion is a pathway for elimination

of drug metabolites but also a

significant pathway for elimination of

the parent drug itself if

the biotransformation is incomplete or

actually does not take place and finally

here we want to measure the element of

adherence

Physicians prescribe medications to

patients

ultimately patients decide whether or

not they will take the prescribed

medication

monitoring for adherence is critical in

the process of drug development

if you are evaluating the efficacy of

the drug you want to know that patients

are actually taking the medication as

prescribed before you make a statement

like the drug does not work well we need

to have rigorous control for adherence

in the context of clinical drug

development

so what are the uses of pharmacokinetics

pharmacokinetics provides the basis for

rational dose selection in Therapeutics

it is essential for development and

evaluation of new drugs we need to know

how drugs are absorbed to what extent

they are absorbed if given orally

where does the drug distribute and again

how is the drug eliminated and what is

the rate of drug elimination

uh pharmacokinetics is also very

important in basic studies of drug

distribution in animals and humans with

the use of pet scanning positan positron

positron

emission tomography

where you can actually visualize The

Binding of drugs to its side of action

now a central tenant of pharmacology is

the dose response relationship

we

carefully study drug exposure response

relationships in order to find the right

dose for a given therapeutic indication

now exposure response of course applies

to both drug efficacy

and toxicity it is important to

understand

the range of doses that are useful

therapeutically

and the range of Doses and resulting

plasma concentrations that may lead to

toxicity with the use of this drug

now there are a number of

pharmacokinetic pharmacodynamic modeling

approaches that have been used to define

this drug exposure response

relationships and you will deal with

that in subsequent sessions of the

course

now linked to this notion of the dose

response relationship is the target

concentration strategy that has been

very useful clinically for a number of

drugs

we already address the concern with

individual variation in drug exposure

when drugs are used in standard doses as

we saw with bioglidison or metformin

so this approach the target

concentration strategy attempts to

individualize therapy when therapeutic

and toxic ranges of drug concentrations

in plasma have been established this is

important

to define a useful therapeutic range and

then to target therapy to that range of

therapeutic concentrations the ultimate

goal is to optimize efficacy and

minimize toxicity

now the first description of therapeutic

drug monitoring that we have on record

is that of Dr wuth

using bromides

and

establishing ranges of therapeutic

concentrations of bromide

as a selective

uh of course

this approach is now used for a number

of drugs and for example

lithium carbonate

in bipolar disorder is administered with

very strict attention to the resulting

plasma levels of lithium so that you

maintain efficacy and avoid some

potentially serious toxicities with the

use of this agent

uh now what drugs are candidates for

therapeutic drug monitoring generally

drugs with low therapeutic index meaning

that we can quickly move from

concentrations that are therapeutic uh

into ranges of concentrations that can

cause toxicity the example of lithium is

a very good example of a drug with a low

therapeutic index but there are many

others like digoxin and some antibiotics

but in any event that category of drugs

is a good category of agents for

therapeutic drug monitoring you may also

be dealing with a clinical situation

where you dont have

if you will physiologic endpoints that

you can observe on an ongoing basis or

biomarkers to guide the dosage you may

be dealing with patients with a seizure

disorder epilepsy where the seizures are

infrequent and of course undesirable

so you use

the range of therapeutic concentrations

if you will as your biomarker to guide

dosage and hope that that would lead to

a significant reduction in the frequency

of seizures

uh we already stated that

pharmacokinetics vary widely between

individuals so if you have a Target

concentration then you can adjust doses

on an individual basis

occasionally we may

use a measurement of plasma drug

concentration to monitor adherence but

there are some issues with this approach

as well

so lets see schematically then what

happens when using the target

concentration

strategy

we have

an estimated initial dose

uh that we administer with a Target

level in mind some drugs need a loading

dose to establish a therapeutic

concentration quickly

followed by maintenance those other

drugs We Begin simply with a maintenance

dose therapies initiated and then we

have to evaluate the patient we need to

see the response in the patient and we

may also measure a drug level and based

on this assessment then we may refine

the dose estimate adjust the dose and

then continue on an iterative basis

to optimize

the range of concentrations that we want

to maintain

throughout therapy

now how do we choose a Target level well

this is an empirical process in terms of

defining what ranges of concentrations

are therapeutic and where you have

minimal or no toxicity

so

we will have

the example of digoxin to address this

topic of how do you define a therapeutic

range of concentrations uh this was a

study conducted uh

in Boston by Dr Smith and Haber

in patients that were being treated with

digoxing

because they had either

congestive heart failure or atrial

fibrillation requiring rate control and

what they saw

looking at a group of patients that were

classified as being toxic or nontoxic

based on clinical characteristics and

electrocardiographic characteristics

without knowledge of the resulting

digoxin levels and this is a histogram

of the distribution of

concentrations of digoxin

in the patients that were nontoxic and

then higher concentrations of the deoxin

being measured in patients that were

clinically early toxic

so on the basis of this empirical

observations then a therapeutic target

range is proposed

in this instance 0 to nanograms

per mL of plasma

it was considered that levels in the

range of to nanograms per ml were

possibly toxic

and patients that had levels of three

nanograms per amount or greater were

probably already having

dejoxing toxicity

but once again

based on

further evaluation of the effects of

digoxin not only on function in patients

with congestive heart failure but now in

terms of survival

after longterm treatment with digoxin

this study that was published in the

early 000s

looking at Patients on therapy for

congestive heart failure

and

receiving digoxin throughout this period

of observation that lasted months and

then looking at Survival on the basis of

The observed

levels of digoxin now there was a

placebo group here

that you see with the continuous line

these patients were receiving treatment

for congestive heart failure but were

not receiving the joking as part of the

regimen and then patients that were

receiving digoxin but now stratified

based on their digoxin levels low levels

of 0 to 0

intermediate levels of 09 to and

high levels greater than nanograms

per ml

now

you see that survival

change

based on the digoxin levels and the

range of digoxin levels that were

measure actually at one month into the

trial one month into the trial uh the

better survival is actually in patients

that have low digoxin levels in plasma

and there is a disadvantage in terms of

survival for patients that continue

digoxing and maintain a level or at

least had a level at one month after

beginning the trial that exceeded at

nanograms per ml

so of course the question is what were

the digoxins levels

well into the trial

we dont have that data but based on

this survival analysis

for the use of the jokes in patients

with congestive heart failure there is a

new therapeutic range that has been

proposed namely 0 to 09 nanograms per

ml much lower than what was usual in in

clinical practice and the benefits may

result from inhibition of sympathetic

nervous system rather than improve

inotropy or improve contractility of the

myocardial

there are limitations for the study we

already pointed that out that no digoxin

levels were done after one month in the

study

and considering that the observations

lasted for months

so

thats how we estimate

a Target level and then in the case of

drugs that require a loading dose and

that was the practice actually with

digoxin

we need to estimate the loading dose

based on the concept of distribution

volume

distribution volume or apparent volume

of distribution a primary

pharmacokinetic parameter so let us use

the example of digoxin

once again

here were plotting the concentrations

of the direction in plasma this is a

logarithmic scale versus time in a

linear scale and were showing the

plasma concentration versus time curve

for detoxing after intravenous

administration

of three quarters of a milligram

single dose this is a loading dose

and now we see that the plasma

concentration versus time plotted semi

logarithmically declines in a

biexponential fashion

we refer to this as the distribution

phase

and then this terminal phase we call the

elimination phase

now the modeling here is plotting the

tissue concentrations of digoxin over

time

and we see that those tissue

concentrations of the joking rise as the

plasma concentrations of digoxin are

declining

now in order to estimate the apparent

volume of distribution for digoxin

one approach is that of the

extrapolation method namely

extrapolating from the terminal phase of

this curve back to time zero and

estimated this C Sub Zero or initial

concentration of the drug

now

that is again one approach to estimating

the appearing volume of distribution

and we are using what we call a single

compartmental model of drug distribution

and elimination we administered those in

our example we gave this dose

intravenously then we have this single

body compartment a hypothetical

compartment where the drug

is distributed and then we are showing

here the parameter of elimination

clearance

and basically what were doing in this

example the volume of distribution by

extrapolation

is estimated as the ratio of the dose

over that extrapolated initial

concentration the Assumption of course

is that instantaneous distribution

occurs we saw that that is not the case

but once again this is one approach that

has been useful in terms of estimating

the apparent volume of distribution

there are other approaches that you will

discuss later in the course the volume

of distribution by area

and the volume of distribution at steady

state

so the example of the joking initial

digitalization this is a term referring

to the loading dose of of digoxin a

quarter of a milligram being

administered and that Distributing into

a single compartment resulting in that

initial concentration of

nanograms per ml you see here we are

doing our proper dimensional analysis in

terms of the

dose that was administered the measure

concentration in plasma in terms of

nanograms per ML and then applying that

principle the dilution principle if you

will we have now our dose

are concentration in nanograms per ML

and we have this rather large volume

apparent volume of distribution of

liters for digoxin uh of course this

does not

agree with the reality of physiological

body fluid compartments but nevertheless

the apparent volume of distribution is a

critical and very important

pharmacokinetic parameter to determine

now lets go back to the process of drug

distribution

uh we saw that distribution in fact was

not instantaneous and that has an impact

on the action of the drug in this case

the chronotropic action of digoxin in

that digoxin slows the heart rate here

were looking at ventricular rate in a

group of patients with atrial

fibrillation with rapid ventricular

response and we have both oral and

intravenous administration this is from

the classic work of Harry gold and his

coworkers in the early 90s

and what were seeing here is a

significant reduction in heart rate

after the intravenous administration of

digoxin but you see that the effect is

not instantaneous the maximal effect in

fact requires six hours before we can

observe uh that uh significant slowing

of the heart rate in patients with

atrial fibrillation so drug distribution

May in fact impact the onset of drug

action that is the rate of drug

distribution may impact the onset of

drug action so

now if we want to continue treatment we

have to select the maintenance dose so

what is the principles that applies here

now in order to estimate the maintenance

those we need to understand the concept

of elimination HalfLife and elimination

clearance clearance being the other

primary pharmacokinetic parameter will

refer to a moment ago

so

simple definition elimination of Life

the time required for the plasma

concentration or the total body stores

of the drug to fall to half of the

concentration or amount present at some

previous time so very straight form

forward definition but again halflife

uh apply strictly to drugs that follow

first order or exponential kinetics of

elimination and we will come back to

this uh in a moment so lets look at

some simple uh equations here uh

referring to the halflife again

assuming first order kinetics of

elimination and the halflife can be

estimated then

as the product of the natural logarithm

of times the apparent volume of

distribution divided by the clearance of

elimination for that drug

the first order elimination rate

constant can be estimated as the ratio

of the natural logarithm of over the

observed halflife

and finally the elimination clearance

can be calculated as the product of K

times their Prime volume of distribution

but in fact a k does not determine

clearance this is one way to estimate

the clearance of elimination

but in fact clearance determines both

the halflife and the first order

rate constant

now maintenance therapy in the case of digoxin now how much do we need to give in order to maintain that therapeutic level that we were looking for in this case nanograms per ml what we need to estimate how much drug is lost over time in this case it was estimated that one third of the total body stores of the joking is lost daily in the case of digoxin the drug is eliminated primarily via the kidneys

so one third of the total body stores at Time Zero are namely a quarter or rather three quarters of a milligram

uh one third of that is a quarter of a milligram so that is the daily loss and that is the loss that has to be replaced on a regular basis so thats how you establish what your maintenance dose should be

now you may start treatment without giving and loading dose

and this is a Brute Force demonstration of the fact that drug accumulation will take place will take place over time until you reach or approach a plateau

after seven doses in this example youre

pretty close to that total body storage

of 0 milligrams

that was established by giving and

loading dose so drug accumulation will

take place

exponentially when you have a constant

dosing rate for maintenance

and you have first order kinetics of

elimination for the drug now there is uh

another approach of course to estimate

the extent of drug accumulation using

this accumulation factor that is shown

here

this parameter

tau is the dosing interval the dosing

interval I mean in the case of our

example it was hours or one day and

then of course you need to know or have

an estimation of the elimination rate

constant the first order elimination

rate constant for that drug now you can

find the derivation of this and other

equations in your textbook

and once again the elimination rate

constant that we showed as in the

equation for the accumulation Factor

estimated as a natural logarithm of two

divided by the

elimination halflife

now lets see graphically what happens

in three different situations here

the first one is that no digitalizing

those no loading those was administered

and the drug is accumulating

exponentially until it reaches a plateau

the solid line here is would be a

situation where a loading dose was

administered to establish a therapeutic

level quickly and then the optimal

maintenance dose was administered over a

period of time actually the maintenance

dose here is the same as the maintenance

those here

now lets say that you gave a higher

loading dose twice the loading those you

gave before but then administer

the same maintenance dose that was used

here and here

over a period of time

the concentration that will be achieved

at the plateau or when steady state is

achieved is the same

so this illustrates the fact that the

loading those thats not determine

what the concentration is going to be at

steady state and now were illustrating

another useful uh estimation namely that

90 of the steady state level uh with

continuous Drug Administration will be

achieved in approximately halflives

for that particular drug

now practically

think about an individual with normal

renal function that is receiving a

quarter of a milligram of digoxin for

maintenance

and approaches the plateau concentration

in approximately seven days as we saw in

our example now think of an individual

with uremia

impair renal function

and consequently impaired elimination of

digoxin the drug will accumulate again

using the same maintenance dose

and you will anticipate that the plateau

concentration is going to be double if

the clearance of elimination say is

reduced by 0 percent but the other

thing that is important is to recognize

that you will not reach the plateau in

the patient with impaired renal function

until later

this is

normal renal function normal halflife

for digoxin this is Imperial function

and a prolonged halflife for the joking

consequently you will not achieve that

steady state concentration until later

in this case in this example until

days of dozen have taken place

so now lets discuss clearance as a

primary parameter in pharmacokinetics

and of course we

need to understand clearance in the

context of drug evaluation and use in a

clinical medicine

now this is a traditional creatinine

clearance equation that you learn in

your physiology courses

that describes the clearance of

creatinine

this is an endogenous product that can

be measured in plasma

and the clearance of creatinine being

used as an index of renal function

and we have this relationship here that

says that U times V over P

determines what the clearton and

clearance is in that context so U refers

to the urine concentration of the drug

or rather of creatinine in this case

V is the urine volume

produce over a period of time typically

the creatinine clearance requires a

hour urine collection

so this is really

a urine

formation rate

and then P standing for plasma

concentration of creatinine now lets

look at this again

and think about the appearance of

creatinine in the urine the rate of

appearance of creatinine in the urine

the E think about excretion or

creatinine d e over DT

and now this is equal to the clearance

for creatinine and the plasma

concentration at that time

so again

that equation that we had before is

really a differential equation in

Disguise

now lets think about the rate of change

of creatinine in the body X being the

amount of creatinine in the body so we

have DX over DT

now being equal to I I being the rate of

creatinine synthesis this is an

endogenous product minus

the clearance of creatinine times the

plasma concentration this would be the

creatinine

excretion rate

at steady state

we can of course discard this term the

actuality

such that the plasma concentration now

is equal to the rate of creatinine

synthesis or is directly proportional to

the rate of creatinine synthesis and

inversely proportional to the rate of

creatinine clearance

uh and lets look at these steady state

equations because these are truly uh

some of the most useful equations youre
going to use in pharmacokinetics so if
we look at continuous synthesis of
creatinine the steady state plasma
concentration of creatinine equals do
endogenous rate of production of
creatinine over the clearance and if you
think about a drug that is being given
continuously Say by intravenous infusion
the steady state concentration is going
to be equal to the infusion rate over
the elimination clearance for that drug
so again one of the most useful
equations for you to keep in mind uh in
addressing uh what are the determinants
of the steady state concentration of the
drug
now we dont
often do creatinine clearance
determinations and collect urine for
hours and a number of equations have
been developed over the years to
estimate the clearance of creatinine in
the case of the cockcroft and gold
equation that has been in use since the
90s and you have these parameters here

that consider age that consider weight

of the individual and of course the

serum creatinine concentration in

milligrams per deciliter now this

estimates based on the cockcroft and

gold equation has to be reduced by

percent for women because generally they

have a smaller body mass

specifically skeletal muscle mass and

that leads to a reduced uh

estimate for women when using this

approach now in this equation or rather

in this slide what you see is that the

terms that are shown in red

are actually estimating the creatinine

synthesis rate that we had in our basic

equation previously

an example of the importance of relying

on the estimated clearance of creatinine

as opposed to Simply measuring a serum

concentration of creatine is Illustrated

in this work by purges and colleagues in

the early 90s they had a group of

individuals that were clinically toxic

due to uh

the use of of digoxin and what they were

trying to see is what was the uh

clearance of creatinine in these

patients as opposed to the serum uh

concentration of creatine and they group

their patients into

individuals that had creatinines in

serum of milligrams per deciliter or

less or individuals that had

greater than milligrams per

deciliter of creatinine and these are

their estimated clearances of creatinine

using the cockcroft and gold equation

what you see here is that in the group

of individuals with uh low serum

creatinine concentration relatively low

serum creatinine concentration 9

individuals 9 individuals out of

actually had an estimated clearance of

creatinine there was less than 0 on

the other hand

the uh

majority of individuals

with creatinine

in serum greater than had a

clearance or creatinine less than 0 so

once again it is important to estimate

the clearance

of creatinine now another approach to

estimating renal function is based on

this equation the mdrd equation many

versions that actually estimate the

glomerular filtration rate not the

creatinine clearance but the glomerular

filtration rate

normalized to body surface area

now youre going to have more

discussions of this equation

in electric addressing pharmacokinetics

alterations in patients with renal

disease

a more modern equation is the CKD Epi

collaboration equation

that is more accurate than the mdrd

equation in estimator in estimating the

glomerular filtration rate and actually

has less bias if the GFR is greater than

0 milliliters per meter per minute

rather once again normalize to body

surface area so back to our steady state

equations if you have a continuous drug

infusion the steady state concentration

is a function of the infusion rate and

the clearance of elimination for the

drug if youre using intermittent dosing

say given the drug once a day or twice a

day or whatever the case may be

this is the estimated mean serum

concentration over that dosing interval

now being equal to the dose over the

dosing interval and again over the

clearance of elimination for the drug

so the steady state concentration

let us emphasize it is not determined by

the loading dose

now once again some drugs require the

administration of a loading dose to

establish a therapeutic concentration

rapidly

but the loading dose does not determine

what the steady state concentration will

be with continuous administration of the

drug

now

the means steady state concentration

with intermittent Drug Administration

is not determined by the volume of

distribution

but on the other hand we need to pay

attention to pick and trough levels

because they will be affected by the

apparent volume of distribution

and this is shown in this example where

the volume of distribution is either

large or small

and the same

dose being administrated administrated

over a dosing interval and you see the

variations in Peaks and trough

but the mean estimated

concentration over the dosing interval

is the same and corresponds of course to

that dosing rate and the elimination

clearance

and uh

an important element to highlight is

that changes in maintenance dose

for most drugs when were dealing with

first order kinetics of elimination

result in directly proportional changes

in the steady state concentration

once again for most drugs that follow

first order kinetics of elimination

and we are reemphasizing our steady

state equations because truly these are

equations you should remember because of

their conceptual and practical use

but some drugs are not eliminated by

first order kinetics and Im giving you

three examples here

phenytoin

ethyl alcohol and aspirin acetyl

salicylic acid these are drugs that

deviate from the general pattern of

first order kinetics of elimination

and lets focus on phenytoin

phenytoin undergoes metabolism in the

liver via this main pathway of

cytochrome pc9 and we have this para

hydroxylated

metabolite

that is generated through this pathway

and here we have an example uh actually

from Dr Arthur Jade Atkinson Jr who had

the opportunity to study a patient with

phenytoin toxicity

very high levels of any Towing of

serving this patient upon admission

and with signs of toxicity just to give

you a reference the therapeutic range

for funny Towing is typically 0 to 0

0 to 0 micrograms per ml were near 0

micrograms per ml when this patient was

admitted with signs of toxicity

and what they did in this very elegant

study is they followed the plasma

concentrations of the drug over time

and at the same time they started

collecting urine

to measure the appearance of this para

hydroxylated metabolide of any time

and you see here day after day after day

that the amount of

this metabolite of any Towing that was

recovering the urine remain relatively

constant the plasma concentrations are

falling as you see here over time

but for a period of time the amount of

the metabolite that appears in the urine

is constant and then we reach a point

when the plasma concentrations begin to

decline more rapidly

and also we see that the amount of

metabolite recovering the urine also

diminishes

what this is indicating and of course

theyre theyre measuring urine

creatinine to validate their urine

collections if you will over time

and over here they started

readministering phenytoin once again

and they see the increase in the level

and then the subsequent decline of the

level what this indicates is that the

metabolic pathway

cc9 that generates this hydroxylated

metabolite orphaniton is saturated is

saturated over a significant period of

time because of this very high

concentrations of anytoin that that

metabolic pathway cannot handle

uh if you will uh

felitoing kinetics actually follow the

pattern of Michaelis mental kinetics

again a concentration over time in this

case given the drug intravenously this

is the rate of change of any time plasma

concentration which does not follow

first order kinetics

represented here or rather determined by

the Vmax that is the maximum capacity of

the metabolic pathway

the Michaelis constant and here again

the

phenytoin concentration terms so this is

a deviation from uh first order kinetics

of elimination so lets look again our

our steady state equations were given

the drug a drug if you will

add intervals orally and this is the

equation we described before for drugs

that follow first order kinetics

clearance of elimination times the mean

steady state concentration

uh in the case of drugs that follow

Michael is meant in kinetics like

phenytoin and ethyl alcohol and aspirin

you need to apply this equation and this

term if you will uh in lieu of these

clearance of elimination term a very

important issue because when you follow

this type of kinetics you lose the

element of those proportionality

here

the patient receiving 00 milligrams per

day of any Towing as a concentration of

0 micrograms per ml in plasma

again the means steady state

concentration

we go up to 00 milligrams

and the concentration already doubles

we go to 00 milligrams per day we have

triple the concentration of any time so

we do not have those proportionality

with drugs that follow

Michaelas mental kinetics of

elimination

and and again this is another example of

a patient that became toxic on a

phenytoin dose of 00 milligrams per day

uh a typical dose if you will but

excessive in the case of this individual

with slower rate of metabolism

that defining the therapeutic dose then

for these patient should really be 00

milligrams per day

and uh one thing of course that arises

as a question is well there is a large

number of drugs that

are metabolized in the liver

so an enzymatic pathway is involved and

yet we do not see

Michaelas mental kinetics for those

drugs so we have apparent first order

kinetics of elimination

and what we can see here is that in

situations where the km the Michaelis

meant and constant for that particular

drug and that enzyme is much greater

than the plasma concentrations that we

will need or observe in a therapeutic

context in the clinic

if the km is much greater than C then we

can neglect this term here in the

denominator such that now we have V Max

over km becoming a pseudo first order

uh rate constant of elimination so the

ratio of two constants of course is a

constant so now this becomes the

equivalent term if you will and their

conditions in which the km for that drug

and that enzymatic pathway is much

greater than the

concentrations that we need to obtain

for a therapeutic response

so I will refer you to the practice

problems that are provided at the end of

chapter in our textbook with answers

provided in appendix so that you can

practice and become comfortable with

these Concepts all the equations that I

have shown are derived again in the

relevant chapters in the textbook

and that will conclude our discussion

today after doing your practice problems

and reviewing the lecture material

if you have questions

please contact our course coordinator

who will in turn uh Implement a

consultation mechanism with the

lecturers in the course so that you can

get an answer that will be posted I hope

I have provided you with an overview of

our discipline a critical discipline in

the context of drug development and in

the context of therapeutic drug

utilization thank you very much