we are fortunate to have dr christopher

chris currently serves as a reviewer in

the division of neurology products at

the fda

his interests include rare neurological

diseases

he also teaches at johns hopkins and the

nih

chris received his md and his phd in

neurological science from the university

of chicago and completed his residency

and clinical fellowship at johns hopkins

he did postdoctoral studies in molecular

neurobiology where he also completed at

the university of chicago and johns

hopkins

im confident youre going to enjoy

todays lecture

good evening

thank you all for coming

um

especially uh

not only those who are here but those

who are online i understand theres

a lot of you um

my name is chris brader

we uh

selfintroduce now i guess so im one of

your colleagues from the fda

um

been there for about seven years before

that i was in industry for about and

im

both an anesthesiologist

and a neuroscientist by training

so like all good

fda talks heres my disclaimer

that this view is mine and actually i

have a lot of one of the benefits of my

industry background is i have a lot of

sort of business things in here as well

as fda things so this isnt your typical

drug development talk

so my objective

is to present to you one strategy

for

the process for submitting a us

marketing application or what many

people call

clinical or drug development

and unlike many talks on this topic i

will also talk about increasing the

value of the approved asset the other

name for that is

life cycle management or post marketing

strategy

this every year i tried to do something

a little novel this is my addition this

year so i typically just teach about

what you do and this is

sort of a quick introduction on how to

do it or how to start a drug development

program

so once

ill say for now once you have a drug

but well talk about the exact timing

later

but once you have a drug the first thing

you do is produce something known as a

target product profile

and that is a

document that contains the

attributes of that product

that are that differentiate it from your

competition and and other products

and from that you develop a clinical

development plan were going to talk

about the clinical development plan

today

if its not in your clinical development

plan its not going to be

something that you can really capitalize

on for your product

and then finally

once youre done your studies and you

have your data that goes into something

known as the labeling or that little

package that the pharmacist has that

unfolds to about this big with 0 size

font has anyone ever read one of those

before

theyre very

many people say that anesthesiologists

read the wall street journal while

theyre doing cases i actually used to

read package inserts which is sort of

geeky i guess thats why im here now

okay so this is

the general strategy of of how you do

that and this of course is an approval

letter its actually a drug i worked on

there so that in a certain sense is your

goal

many people want to know

when should i start

working on my target product profile

when do you think that would be

when does a drug development team start

this

any

any guesses

right

and even

before the beginning because once you

synthesize your drug

and you start testing it you cant

change it at all all you can do is study

it

so before you actually pick a drug

candidate you need to know what you want

what sort of attributes because the

the scientists the drug discovery folks

can actually do something to help you

pick a drug that actually does

what you want

while the intent of this lecture is not

to go into the discovery process in one

of my lifetimes

i worked with the discovery and

marketing folks

at that early stage and i thought it was

really fascinating so ill show you some

slides about how they do their

their business or essentially

you know where do new drugs come from

so

theres many is anyone here actually in

the industry does anyone work in

discovery or do you consul

so its really a fascinating

process at least one of the places where

i was had this

machine called the haystack i think it

was and they had millions of compounds

and you could develop an assay

and then screen all those compounds for

that

and then you would do structure activity

work

so

thats for new molecular entities

you do this sort of fishing you can do

structure activity relationships

etc its very chemistry heavy its very

exciting every week to have chemists

come in with 0 compounds and they show

you all the things theyve done

biologics

theres

just a wealth of places where drugs can

come from there

and reformulations are also a very

popular

type of drug development

and the formulation chemists come up

with all kind of things that make the

that modify the profile

of the bioavailability

of the drug

there so this is a picture of that high

throughput screening process

once a candidate

is selected

from there it goes through something

that different companies call it

different things

where i was they called it development

lead selection

lets say you have four candidates

so the first step it might go through

receptor binding

you might find it binds to a target you

dont like the serotonin b receptors

somewhat unpopular

so you might knock out certain

candidates from there

might do some early bioavailability

studies and in animals

and also

pharmacodynamic screens keep knocking it

out

you might do some preliminary toxicology

work

as well as

whats known as admin

which is the in vitro pk

absorption distribution metabolism and

excretion

and you might not want certain

admin profiles so you can knock that out

and according to this screen then

you would pick

molecule b

and then you would have a development

candidate

in industry the popular

expression is throwing it over the fence

or something like that it actually takes

a lot

for a molecule to be born to get into

the clinic

for all those that fail in the clinic

thousands fail

before this step

so this is your time

before you do this to think about what

assays do i want

so i can get closer to my target product

profile for example

back when i was doing this antipsychotic

drug development was very big and there

was a theory at least that binding to

histamine receptors led to obesity so if

that was in fact true you might put a

histamine receptor screen

in here and throw out everything that

binds a certain histamine receptor or

what have you but if you dont do that

once you pick that drug

youre stuck with it um

so the time to work on your target

product profile

is

at literally at the beginning soon as

you say i want to develop a drug thats

when you do it

so

like most most lectures they say

say what you want to say say it and then

say it again well this is the punch line

for the whole

lecture this is

a map of a strategy for

drug development its sort of the most

typical map it gets modified extensively

depending on what type of drug youre

developing

but if you understand why this is the

typical map

its very easy to modify to shorten you

might need to add something what have

you so what im going to do

in the bulk of the lecture is to derive

this map

theres a wisdom

in drug development lecturing that you

should start at the end

okay and work your way forward when i

first gave this lecture i used to do it

from the beginning and work my way the

other way

so now i do it i go backwards and all

which makes sense too its uh

whats the least that i need to do

to march backwards from each step

but im not going to talk through it now

but

slowly but surely were going to build

this map youre going to get a sense

of how to

develop most

most drug candidates

so these are the aims for drug

development

if you had a lecture

on

how to apply

for a marketing application

someone would tell you that the

applications either called a bla

biological license application or an nda

new drug application

and theres a common

form that companies fill out in that

application its called a common

technical document and the three

major functions

that

review

that at the fda

are the chemis

cmc

the pharmacology

toxicology folks and the clinical folks

and since my lecture is on clinical

development programs i am only going to

talk about clinical

so heres the goal for clinical

you need to establish efficacy

and safety for a drug or biologic

in a dose range and schedule

that provides an acceptable risk benefit

relationship so well talk about each of

these

components

and

before we do i thought i would show you

where the bar is where is it

where is that derived you know how high

do i have to jump to get over this bar

and this is from

the actual law

upon

which almost all of drug development is

based

the food

drug and cosmetic act

of 9

um

and theres actually six

six ways to not six ways to fail

and this he or she refers to the

commissioner if they always refer to the

commissioner will do this or that

or their designee

so there are six ways for the

commissioner to refuse it and if you

look at this

one two and four

are all different ways of saying you

have to demonstrate that the drug is

safe

and

number three

is a chemistry rule

number five

is the rule that talks about efficacy

were going to talk a bunch

about this phrase here substantial

evidence and what that means

and then six is about patent stuff and

well leave that to the lawyers

so first lets talk about efficacy its

the first part of that statement you

know

i think of all the phrases

in

in the regulatory field the one you

would think is the most discussed the

most talked about

is efficacy

because you actually cant study safety

unless your drug is efficacy you can

always pick a dose for your drug

thats safe right if you have a

billionth

of a pharmacologically effective dose

thats not going to have many side

effects

but if you bring that dose up to where

its actually

affecting the pharmacodynamics you want

thats when you start to see toxicities

so efficacy is very important

and as it turns out probably the least

defined and discussed word in the

regulatory literature is efficacy its

actually very hard

to find a definition

that really pins it down

in fact when it does discuss it it talks

more about something called

effectiveness which

youre actually taught

you know when youre at the agency is

something different

but

efficacy

essentially is just the power for the

drug to produce an effect

and the effect that it has to produce is

the one that you propose in your drug

labeling

okay

and well get to that more when we look

at the substantial evidence

wording

effectiveness on the other hand is a

more realworld

definition how well the drug really

works

in real life situations thats something

that the

the payers and the

pharmacies are actually more concerned

with and can you in some staged event

demonstrate

that you can produce pharmacodynamic

effect

so why do we care about efficacy

well

you need to make sure the drug works

and importantly

much of drug promotion is based on the

labeling

so

so efficacy is very important

and as i just mentioned you need to

assess safety in the context of an

efficacious dose here are there any

chemists here

i actually my first life was a chemist

paracelsus was like the

father of chemistry

there and the first uh credited with

being the father of toxicology also

and then as i mentioned some authorities

are particularly interested in

effectiveness

even if you can get a drug approved that

doesnt mean they want it on their

formulary it really needs to add

something

so this is the actual legal definition

around

efficacy and as i mentioned this term

substantial evidence is very important

and the law

which believe it or not

this part didnt come around till the

0s around the thalidomide

events for those who are fans of history

said that you need evidence from

adequate and wellcontrolled

investigations with a the s is very

prominent here including clinical

investigations

that the drug will have the effect it

purports

under the conditions in the labeling

and then later it was added

that if the secretary so my apologies

its not the commissioner its always

the secretary or the secretarys

designee

uh if the secretary determines

based on relevant science one

trial

plus something known as confirmatory

evidence which is evidence which can add

to a clinical trial

such that you believe that the drug

actually has the effect

it purports this came around

99

this rule right here

so the critical

thing here is that to have substantial

evidence which is

essentially the evidence you need

to be convincing in a marketing

application

with no other evidence you need two

adequate and wellcontrolled

trials

so

and this is what adequate and

wellcontrolled means and this right

here the last slide was from the law

this is

from the regulations which are derived

from the law so

from this document right here

so this defines the type of trials that

one looks for

to provide substantial evidence

and as you read this has anyone here

ever helped write or read a clinical

protocol

so you can

youll see this in all the protocols

right so you have

different treatments objectives

inclusion exclusion criteria

uh methods of randomization

also

other

ways to minimize bias like blinding

singleblind doubleblind etc

and

the the outcome measures or endpoints

are welldefined

and then a

analysis plan so these are all things

you sort of take for granted in a

protocol but they have their their legal

basis

so now weve covered the first of those

requirements efficacy

so the rule is unless you have

contributory evidence which can be other

clinical evidence sometimes

nonclinical evidence suffices you

should plan on doing two adequate and

wellcontrolled trials especially for a

brand new drug

reformulated drugs

and of course there are many other

exceptions but if all youre doing is

making the drug a controlled release and

its already been approved as an

immediate release

of course you know that the molecule

itself has an effect so that would be

contributory evidence so you more than

likely would not

need to do two trials

so

weve established that so now were

going to find out how do i get to that

stage of two adequate and

wellcontrolled phase iii trials

before we do

there is anyone here in clinical

pharmacology

no one this time well youll recall

was anyone here for dr pecks lecture i

think i recognize some you know from

last week well hes hes a clinical

pharmacologist very

big advocate of studying clinical

pharmacology

there are some

clinical pharmacology studies that you

need even to get the ball rolling

okay the very first things you do and

well talk about them in a minute but

there are some that you typically

dont do until the very end

and

one reason is because you want to make

sure the drug actually works before you

do some of these

because these are horrifically expensive

studies

and also if these patients arent your

primary patient

that the indication is for

you may not need these studies to

conduct the phase study but youll

eventually want the information in your

labeling

and chief among them are these studies

the renal and hepatic

impairment studies

drug interaction studies

so if your early nonclinical

data suggests you have a drug

interaction youre going to want to do

those

those studies and

many act many people actually say

you want to do that before your phase

threes because if youre worried about a

drug interaction

you have to exclude those people from

your phase study and you dont want to

exclude anyone that you dont have to

from a phase study because that will

limit the population you can study which

will slow you down

and also give you a more restricted

labeling

okay but very often they are excluded

from phase studies because you arent

sure if the drug

works yet so to do these

programs would be

you know not not a good business

decision

usually unless the exceptions are

if your drug

is for these patients you you want to

know that beforehand

and also if you have a strong signal

for any of these

its best to study it as soon as

possible if you have if youre

developing a drug for psychiatry

and you suspect that it interacts with

cytochrome the sip many other

psychiatry drugs were metabolized by

that so you would be well advised to

study that

very soon

so you could either you might even kill

the drug

based on that

because

if your competitors dont have that and

you need to have a very complicated

dosing

you want to know that right up front

so now we have this part of the map

were going to sort of draw the map

backwards

all right so

new drug application filing

two adequate and wellcontrolled phase

three studies

and then these clint farm studies

so going

back here the next part of the map well

talk about

is this concept of a dose range and

schedule

very important

so

question is how do i get to my two

adequate and wellcontrolled studies

optimally you would do phase two studies

and

to be specific phase to be and for me

personally

um

phase two is any study that involves

patients where the object is to study

the effect of dose on either safety or

efficacy

and

the b refers to

uh

studying typically studying efficacy is

is the primary objective

phase a studies tend to be for

safety questions

all right so phase two i often say its

the lone wolf

very unloved

because its not really strictly

required

in the regulations no one says you have

to do a phase two

um

but

it could be very its

it could be very wise to do it its

always good to know more

about your drug before you spend about

three or four hundred million dollars on

your phase program but i would have to

say

many programs dont do phase studies

so

and they dont do them because these

trials are almost as long and expensive

oops

as phase studies

the question is can they be

registrational and the answer is you

know they can if you prespecify your

analysis plan

the difference typically is that you

dont have as many subjects

in them and you really are

exploring but if your drug really works

well and you happen to get a positive

study

especially in rare diseases no ones

going to quibble between whether it was

called phase two and three

so they can be

registrational

and there are cases where

it doesnt make too much sense to do

phase studies such as when youre

doing modified release

formulations with wellbehaved

pk in your molecule if you have a drug

that typically doses at 00 milligrams a

day

for the immediate release

um

youre probably safe not doing a phase

two study youre going to want about the

same

the same dosage now there have been some

modified release drugs

where

they only had like 0 percent of the

bioavailability

and so after they did their studies they

bumped it up but that was all based on

pk

pk results

the other thing you might consider is

one of the main reasons to make a

modified release drug is to sort of cut

off the cmax to make it more tolerable

so you might actually be able to put

more

drug into the

into the pill than was in the immediate

release it might be more tolerable with

a slower

absorption but you need to make sure

you have all the nonclinical

work that supports that

this is a

fairly famous example of when phase two

was not done in this

uh

study for this drug chlorthalidone

um

it was actually marketed before much

dose exploration was done and had very

bad side effects and then a dose

response study was done

and it was seen its that chlorthalidone

as an antihypertensive drug

uh was actually seen that there is a

sealing effect

on the fall

in blood pressure and just pushing the

dose higher was just increasing the

toxicity so

um the time you

whats the expression

never

a better you know you need to make a

very good first impression its very bad

to launch a drug twice

especially if the first time you

launched it it had a bad safety profile

given the cost of it it makes sense to

do it wisely

so this is

this is a good rationale for doing phase

two so you understand the dose of your

drug

these are different types of dose

response

measurements you can look for one is the

maximal tolerated dose

which well talk about in a little bit

thats often gotten in the second study

of the whole series which ill describe

called the mad study

you might also look for the minimal

efficacious dose

you want to look at the curve

that leads up to that is it a very

steep curve or a very flat sort of curve

and also titration is incredibly

important and well talk about

the cases that it seems most important

almost toward the end of the lecture

so now we have this part of our map

built

right nda

from phase three

and weve done our phase two b studies

and these sort of late

clin phase

studies

so the question is now how do i get to

my phase two

so what happens

at phase two that i need to prepare for

well phase two

[Music]

has extended exposure of drug

can have many subjects into the hundreds

people theyre actually patients right

phase two so theyll have different

diseases and concomitant medications

and

so to do all this you need to really

understand

your drug and also some people dont

think its wise to go from a two week to

a year

exposure of the drugs so they put

something

intermediate and in case theres some

toxicity

associated with extended exposure

but but especially since this is a

clindfarm course ill emphasize that

its very important to really understand

your drug before you go into patients

because they can be very

unpredictable

so now weve been working backwards in

the scheme now im going to do a

an end around and were going to

actually start from the very beginning

all right and this is the beginning

of all the clinical pharmacology studies

did you talk at all about first in human

studies

before all right so ill not go too slow

on that so of course the first study in

humans

sometimes called the first in human

study also called the single ascending

dose studies

and to do that

at least in the united states if thats

your first study you need to submit an

investigational new drug application

which includes

for the most part nonclinical studies

this is the guidance

carl peck talked about guidances this is

a great read even a clinician like me

can get through that document its

written very well

you also need the supporting chemistry

documentation

and it gives you some safety and

tolerability

uh information only for a single dose

and

also data for pk modeling so as dr peck

explained modeling

has a very important place in drug

development you really start getting

data right here

and what it allows

is

this study is called the sad study after

youre sad then you can get mad multiple

ascending dose study

and

this you typically pick three or four

dose levels

and

push the dose

until its not really tolerated and the

reason you do that is because you dont

want to go into phase three not having

known what the top of your tolerability

curve is you dont want to under dose

you know because youll never be able to

go you will be able to go back again but

phase three studies are terrifically

expensive

and when you tell your boss that you

didnt pick the optimal dose you

probably wont be the one whos

repeating this

all right just im sure youve had this

what you get from a single ascending

dose study this is a

time

curve for exposure you get the area

under the curve also known as exposure

the cmax concentration max

the tmax right here various metrics

you get

as i mentioned

typically you go on the next study is a

multiple ascending dose study

prerequisite would be a single ascending

dose study plus supporting nonclinical

information

and this really gives this is one of the

most valuable pieces of information your

maximal tolerated dose so you go up to

where you have a toxicity you dont want

and go down

and thats your maximal tolerated dose

its not the dose that gave you the

toxicity

and

critical pk data one of the most

critical ones here is known as c min you

notice i didnt have that on the single

dose the semen is also known as the

trough level its the lowest level

before you take the pill again

and for many

drugs and classes is thought to be

really the critical

plasma level like antiepileptic drugs

the semen

needs to stay above a certain

floor level once it goes below that you

start having seizures again

whereas other drug classes you think

about different things like

antimicrobials

you think about the cmax more you want

the drug to go up and spike kill the

bugs

come down like that

and thats one reason why some modified

release

antibiotics dont always work as well

because they dont have that

spike

oops

so what the mad study gives you is it

helps you select the dose for phase two

and there are some studies you need to

do in clean form where you need to know

the top clinical dose

such as a food effects study

and a qt study i think youve been

introduced to the qt study before is

that right yeah

and this is what the data looks like

this is actually

data from two different types of

experiments here we see with the

unfilled circles what a

four time a day drug looks like

heres the cmax here are the cmins

and this is a modified release drug

so it has its taken once a day

and it has

one peak

see how the semen

is a little lower than that

so that could be a little concerning

depending on what this drug is for

if this is an analgesic drug youre

typically not as worried the pain relief

level is often more related to the auc

but if this is an antiepileptic drug

your

difference is about

0 to 0

okay so

that amount may or may not be critical

this is your mad study

all right so now we have our map again

all right and these are actually this is

the beginning

and this actually isnt quite the end

um well get to the end soon

does anyone know

the phrase for what the

the shortest series of studies to go

from beginning to end is called

its a expression people like to sort of

throw around these days

its called the critical path

so the critical path those are the

studies that define your

your timeline

all right because

these studies here you can do almost any

time right you can shove them forward or

back but you start with sad

and you go to nda theres actually one

more thing here so its not really your

critical path but

any slip whoops

any slip up

of the timeline of any of these studies

and the whole project timeline

shifts forward whereas if your drug

interaction timeline slips its not

going to have as big an effect

so when youre the person responsible

for the critical path theres a lot of

pressure on you

so other supporting clin farm studies

are listed here

well

sort of quickly go through them

the thorough qt study which i think dr

peck may have explained

this is the arrhythmia torsade

right here

generally if you see that on tv

thats not a good thing you dont want

your heart to do this it should really

look like this

right here

so the qt

goes from here to here and that gets

prolonged and then the heart just

decides to do what it wants to do and

this is one thing it does and there are

certain drug interactions that are known

to cause this so the fda is very focused

on that

others food effect study

food effect study is a type of study

called a

bioequivalent study bioequivalent

studies

are hypothesis

driven studies where you want to compare

one condition to another so the

condition here

is fed versus fasting youre actually

testing a hypothesis

the hypothesis is that theyre no

different

okay

dose linearity

you want to know that theres a

predictable increase in exposure

with dose this is another bio

equivalence type study you actually

normalize

the data for the dose and then do bio

equivalence calculations between the

different dose levels because they

should be the same

dose proportionality

very often theres if you have three

pill sizes one two and four milligrams

you want to make sure that four times

one is the same as one times four

and youd think why wouldnt they be

well some pills have such a dose range

that you actually need to make the ones

at the top end a little different than

the ones at the bottom end you put

different uh things in there called

excipients which are the nonactive

parts

um

because of the

the difference in the strength they

could actually be different formulations

metabolism studies

um

if you were in my it also teach drug

development at hopkins in their online

program and usually i have a slide

before this that shows a rat in a little

metabolism cage and they collect its

feces and urine and all that

and while we dont quite do that with

humans this is sort of the analogy that

they actually give humans radioactive

drug

and they collect various fluids

and they look at the metabolism of the

drug and this is done very early in the

process because you want to have a

handle

on how the drug gets metabolized

actually this is something youve

probably seen from experiments here

whole body autoradiography

in an animal usually done as tissue

autoradiography

and this is the analogous

situation in humans its not a required

part

of any development program but it may

inform about whether the drug penetrates

into the brain

all right so now

weve added a few more ornaments onto

our map

right here and were going to get to

the very last part of this map and that

is

safety

so what is required for safety

i wont read this to you but there are

actual numbers

that are given for how many patients

need to be exposed and this is not

an fda specific thing these are actually

part of rules

from a group called

ich or international conference on

harmonization thats

really an international

agreement which is good because now drug

development is more global so it allows

material from one application to be

usable

throughout the world

you can see though

that theres or for chronic drugs you

need to be treated for at least a

hundred

for

a year and all this

is subject to some reason i did

anesthetic drugs for a while the

regulation of them and as you can

imagine something youre only going to

get once

or twice

you dont need to keep giving for a year

so

generally use some clinical sense in

these numbers

so

but as a base case for chronic drugs

diabetes rheumatoid arthritis pain what

have you

you need 00 subjects exposed to a drug

00 for months 00 for a year

and the number can change its usually

not in the direction you want depending

on if you find something that needs to

be studied a little

more and very often people do these

studies following their phase three

studies called longterm extension

studies that are tacked on open label

studies as compared to doubleblind

it is actually very expensive to blind

medications clinical supplies for a

clinical trial are very expensive and

theyre really hard to coordinate if you

might imagine especially if youre

making drug cards up for the whole world

right drug cards in russia england us

its just an extremely complex process

so these longterm extensions are for

the most part open label

and therefore

finding

if you have

side effects which we call adverse

effects

that occur with prolonged exposure

so i note that right here

visits are often less frequent you often

have

you know

you dont do all the pharmacodynamic

assessments

and actually these are not good for

uh studying efficacy or pharmacodynamics

because theres no blinding so everyone

knows whos on

what drug so theres a lot of

subjectivity there

this is a schematic diagram of what that

these studies look like you go from a

doubleblind randomized control trial

to an open label longterm extension

study

these little lollipops are the visits

you can see

during the study active versus placebo

the visits are very regular

and very frequent

and then at the end of the randomized

control period

and this is just one way to do it

theres many ways to do it

you down titrate the actives you up

titrate the placebos to a common dose

now you can break the blind

right because everyone is on a common

dose

and then

once they get once everyones on that

dose

then its up to the physician whos

their actual doctor to adjust the dose

they can go up or down or whatever they

want

so this is how these trials work you can

also feed more

drug naive subjects in at this point

because you may need more subjects to

meet that 00 subject exposure

so now we have the complete map all

right this is the map you had

at the beginning it has the critical

path

and you can see this is the element that

was missing

and the clin farm studies these two

clint farm studies are critical path

studies the others typically

are not

notice i put a little asterisk by

thorough qt

if theres a signal somewhere in your

nonclinical

that you need to be worried about the qt

prolongation

that study is moved forward but if

youre not

so concerned about it from your

nonclinical data that like the these

studies here

is done later because this is also a

terrifically expensive

uh study and also if its supposed to be

done at the top of the clinical dose

range you dont want to go in with a

dose early on that may not be your top

dose because then it wont be as useful

for what you need it

for so heres

my one slide on biologics biologic

development is

to a large extent like small drug

development but there are some important

differences because they are biologics

and

the difference is so first you have a

first in human

you often

well you should have a multiple

ascending dose study

this is a very subtle difference the

first

study

of small drugs

is based on animal studies based on the

no observed adverse effect level or no

ael

okay but for various reasons

in biologics use a much more sensitive

level than no observed effect level so

its not just an adverse effect its any

effect does anyone know why

we have that difference

may have happened before your time

so

i dont even know how many years it go

it was now but i remember hearing about

it on the radio so maybe like seven

eight something like that

years ago theres a

an english study i think and they dosed

everybody at once on something where the

noel predicted no toxicity and everyone

went into organ failure

in that study

the

you could look it up its called the

tejanero case

tegen something

well that also recently happened

and why it was is because the toxicity

studies were done in monkeys

and they werent they didnt have the

same immune

response that humans had so

if you based it on the effect level it

was way higher than it should have been

so ever since then

its been based on

the noel and instead of reducing the

level by 0 which you do with the no al

its reduced by a hundred so

everything is meant to be safer of

course

we still have things like the

the france

event

so ive actually put two additional

studies in here based on a general

principle

and that is that

if you give biologics well biologics

have two special properties

one is that they tend to

outlast their presence in the

bloodstream

whereas small drugs generally by the

time theyre eliminated which is five

halflives

plus or minus some

the effect goes down but biologics

may have a

prolonged effect so you really need to

understand what is the duration of

effect

and the second thing you need to

understand is

that

a lot of the toxicity of biologics

happens when youre just giving the drug

when youre administering it

and the faster you put it in the more

likely you are to have these nasty

infusion reactions with cytokines

released and

people draw these charts with arrows all

over and

its just really ugly one class i have i

actually show the pictures and its its

not pleasant before dinner

so you really need to understand how

fast you can put the drug in and how

high

you can put the drug in because just

like a small molecule

if you can put it in safer you might be

able to put in a higher level also

but its definitely bad news if you put

these drugs in too fast because you get

cytokine release

and its not not too good

and then after that

some of the

clint farm studies are different so

um

you know you dont typically need to

worry about a food effect because youre

not eating the biologic

like the pill its generally going in iv

and many of these are broken down

like the proteins in a manner different

than small molecules so you may not need

to do the hepatic impaired study

but its a case by case really

so thats

basic drug development that is one

scheme

of how to do it and

you can do drug development a million

ways but it helps to understand why the

basic scheme is laid out the way it is

and then you can decide what you want to

take out or add

now ill talk a little bit about

postmarketing development its really

when much of the work actually starts

in a drug development i was on a one

team that had about 0 people

before the nda and about 00 people

after the nda

you know i started five trials at once

on this drug its just

its very exciting

so these ill talk now about some of the

different options

oops

these are just some you dont see a lot

of data

about the business of postmarketing

development i think people dont like to

talk about

drug development in general

it just seems like something they want

to keep in the back but heres

what little information i could find i

throw on a slide here these are the

different ways

you can prolong the life

of your drug

first always of course the litigation

citizens petitions you can have pricing

strategies

pediatrics new indications new

formulations

you need to start on your next

generation of drug

and combination drugs and this shows

based on a survey

how different companies attempt to do

this you can see one of the main ones is

new formulations

okay something the patient can actually

benefit from

this shows return on investment

pediatric exclusivity now especially

that its given six months of pediatric

exclusivity

can amount to a pretty good chunk of

money

lipitor made about 0 billion dollars a

year so five billion dollars will buy

you something right itll fund

at least two or three new chemical

entities if spent well

uh modified release formulations are

very popular there are some companies

that do nothing

but this

right very

cool if youre a chemist to be involved

in this they have these

drug with different

types of polymers around it and they can

pretty much reproduce

any profile you want they can even make

a controlled release profile that looks

on a daily basis like an immediate

release profile

so instead of taking two or three pills

in a day to get the immediate release

profile you take one

and they have like five or six different

beads in them and then all of a sudden

that bead does its thing and releases

drug and

and so forth its actually

out on the market now

and the reason you might want to do that

is because there is evidence especially

with some gproteincoupled

receptor effects

like for amphetamines with adhd

and opioids with analgesia

that a sort of smooth release profile

actually causes receptor down regulation

so you dont want something nice and

flat otherwise your receptors go to

sleep you want to kind of spike it up

and down

this is the picture i showed you before

so we went from a four time a day to a

once a day

your main concern is this drop in the

semen

sometimes thats critical and sometimes

its not but believe me any difference

between the two

the

clinical reviewer the clin farm reviewer

is going to note and youll have to

rationalize why thats not an issue

here i just have some notes on how

the development program for a modified

release is different

generally you need to do less toxicology

work especially if the immediate release

was done

before

your real goal in

modified release development is either

convenience because it is important to

its much easier to have a once a day

drug than a four time a day drug

if you have a kid and you try to give

them a pill even a once a day drug is a

pain four times a day will put you on

the mat

but

also important you generally get

increased tolerability

for the side effects that are pk

dependent

now if my drug has a warning

about something like hyponatremia or

something like that thats generally not

a side effect thats sensitive to the pk

of the drug its just a property of the

molecule so if i have a warning for that

with the immediate release theres a

good chance im going to have that with

a controlled release

also things like anaphylaxis and things

like that

but certain things

uh especially with cns and gi drugs like

nausea headache dizziness those seem to

those side effects seem to have a very

nice response to controlled release

drugs

and they are also important for the

patients because no one wants to feel

nauseous

or get a headache

is just a chart

with more detailed information one of

the

some differences ill point out you

dont generally do a single ascending

dose in a multiple ascending dose

because you already know

what the tolerability and safety of the

drug are

but you need to test a number of

formulations

so you do that with a single dose with a

bunch of formulations you might have

one arm for each that has a pilot fed

because having a food effect with a

modified release drug can be a drug

killer so you want to know if theres a

big one youre not going to have much

sensitivity here but if theres a

whopping food effect you want to know on

the first study so some people do that

and then

you dont need to do a

multiple ascending dose but you do with

the final formulation you typically

do a multiple dose

and

you might even put as one arm the

immediate release comparator

which takes care of this requirement

which is actually a regulatory

requirement to study that

and then youll see

these are

are things you had to do before with the

immediate release

and this is a very important one

does anyone know the story about alcohol

dumping

turned out with one of the

one of the first uh controlled release

opioids

that if grandma had her opiate with a

scotch it dumped

okay so all the opiate came out

and thats thats not a good thing

so now the alcohol dumping is tested as

a regular feature

of a controlled release

of formulation chemistry first its done

um in the

in the dish

you know with paddles and different

concentrations of alcohol and then if

theres a signal you actually do a

study in humans with the pill and

alcohol which i guess probably gets a

lot of volunteers

pediatric development

is based on two

laws

and actually they should be reversed

this ones known as priya thats the

stick

okay thats the law that says you have

to do studies in pediatrics if your

indication

is amenable to that so thats part of

the nda process you need a plan

in your adult nda

you know to either have the data then or

say that those studies are are ongoing

are going to be

done

and then the carrot is best

pharmaceutical act for children this is

the law that gives the

six months of exclusivity

they have different

regulatory features between the two

the two laws

that ive listed here

for example differences not required for

orphan indications for pria

etc this wr written response this is how

the fda requests

these uh bpca studies

these get reviewed in a standard fashion

these are

priority etc slightly different

regulatory features

one way to think about pediatric studies

i often say they come in three flavors

some are expected

with your nda its hard to make a case

for a drug

for epilepsy or asthma that you dont

need that labeling for kids

on the other hand

als or parkinsons its hard to make a

case that you need to do those studies

although

i didnt

know this until today it turns out

theres a pediatric variant of

guillainbarre syndrome so

you know it depends on the epidemiology

of the situation

and then something in the middle

are diseases that

kids do get

but its not

you know necessarily the fact that they

typically start in childhood

so you can generally defer these studies

till after

the adult

indication is approved youll just have

to do them afterwards

and then of course you need to do

juvenile talk studies typically

the typical program you would do

heres that phrase i mentioned earlier a

phase a study theres many ways to do

this though

where your main goal is to get pk

intolerability

and

then

a phase study

and some of the issues you need to be

concerned with weightbased dosing is

always difficult

giving placebos to kids is

you know its really a casebycase

basis that needs to be worked on

theres a whole part of the ethics laws

that deal with

using children in studies thats very

complicated so you need an ethics

consultant

to wade through that

overthecounter drugs i always thought

overthecounter drugs were pretty cheap

and didnt really net a lot of money but

uh it turns out

if you look at the

over time

you know they actually make

you know quite a bit toothpaste alone

makes billion dollars

all right which is sort of like liquid

sandpaper

and all its its amazing so thats why

the companies and

generally its a lot less work

overthecounter drugs than a

prescription drug so theres you know

less payoff at the end but much less

heartburn in the beginning

speaking of heartburn

theres a billion dollars in it

generally overthecounter drugs need to

be selfdiagnosable

um patient needs to

be able to determine when the drug is

appropriate needs to be able to give it

to themselves

and need to know when they need to talk

to a physician one thing ill say about

overthecounter drugs has anyone ever

gone to the drug store and read like the

box

and all its imminently more readable

than a prescription drug label its

almost in a geeky way its sort of

enjoyable to read because you can really

understand it its

much harder to read a prescription drug

package insert so ill give

give some kudos and credit to the folks

in

in otc because its very usable

uh yeah most of the studies

in

overthecounter

are related to

how much does the patient understand the

labeling versus does the drug work a lot

of label comprehension things

in a development program

generic drugs again you always think you

know generico must be pretty cheap they

dont make money and all that and all

oops

lots this isnt even a very new

slide its probably much higher than

this

but generics is a pretty good business

and the deal with generic drugs the

labeling will be the same

as whats known as the innovator

drug

sometimes though

there exists like a patent thats still

going on and then the fda will do whats

called carving out that part of the

labeling

lets say a drug has two indications and

a generic once to go on the market you

know its possible to carve out the one

indication from the labeling and itll

look identical to it except not with

that indication

if its a use patent

for example

all right

okay so in summary

clinical development is the part of the

program where we talk about the dose

relationship to safety and efficacy

and evaluate the risk benefit

considerations i really didnt talk

about risk

benefit considerations its a whole

lecture unto its own

because this is a clint farm course

the clint farm part of the program as

carl peck said

its a driven by specific questions

about how the drug and the patient

interact

they allow

all the other studies to go on because

if you dont really understand your drug

you really shouldnt be dosing hundreds

of people

efficacy

actually didnt even address this

efficacy

you can produce an effect and prove it

but that doesnt mean that you really

have a drug

um

it really needs to be a clinically

meaningful

thing okay clinically meaningful

hypothesis okay

and then um also i didnt explicitly

talk about this but postmarketing

planning

should begin in parallel with the

registrational program

and the oops and actually that fell off

but once your drug is approved is not

the time to start your postmarketing

program because these trials take years

and the planning takes years as soon as

you know your drug has an effect

at all

then all of the post marketing planning

and execution should be started

at that point

just like the tpp you front load

everything and then

by the time your first indication gets

approved you have all your other trials

ongoing

and in rapid succession youll be giving

your sales force more and more to talk

about

um

and so that thats what leads to a very

successful drug development program

and with that ill take questions

[Applause]

you