we are fortunate to have dr mansour khan
as professor and vice dean of texas a m
university college of pharmacy
prior to joining texas a m in 0 he
served as the director of product
quality and research and senior
biomedical research scientist at cder at
the fda while at the fda he led the
research and review teams to promote
manufacturing science of new generic and
biosimilar drug products
dr khan received his phd degree in
industrial pharmacy from
st johns university in new york he has
published over
peerreviewed manuscripts informa
pharmaceutical formulation and
manufacturing science
dr khan has served as fda representative
to the world health organization
the united states pharmacopoeia the
european medicine agency
darpa the national institutes of
pharmaceutical technology and education
and the international pharmaceutical

federation we hope that you enjoy

todays presentation

hi

greetings everybody

its uh

great to be with you all my name is

mansour khan im a professor and wise

dean in texas a m university

and in texas we greet people by

saying howdy so howdy everybody so first

of all i would like to thank the

organizers dr lisa cardes and rebecca

wong for inviting me for this

presentation

and let me pull my presentation here one

sec

well now you should be able to see my

screen here hopefully

so the title of my presentation is

considerations in the development of

biologics so i have a background in

product formulation and and

bioavailability bio equivalent so ive

been a clinical pharmacologist in food

and drug administration before

but i think the

the presentation will focus more on the

development and regulatory aspects of of

the biola biologics so as you can see

there are things that we miss as

scientists and i see a lot of

discoveries that that theyll miss

they dont see the light at the end of

the tunnel and so hopefully with this

presentation youll youll

youll focus on some of the things early

on so that your developments and

discoveries lead to some meaningful

product development

so a lot of it will be fda the

development process and then the

biologic characterizations the protein

characterization right thats what i

will deal with so

the learning

objectives actually instead of saying

outlines because this is a part of the

course it is pretty much

uh the learning objectives of the

outline the broad outlines here lets

lets differentiate between the laws the

regulations and the guidances that will

help us look for appropriate information

when you need as you are developing

protein formulations right so lets

outline the fda drug approval process

and describe the ind phases and various

types of inds and we will describe the

various types of fda meetings

uh and ill tell you why why these

things are important once we have these

backgrounds then its easy for us to

understand the development of proteins

as both a drug substance as well as a

drug product

so

where does the fda derive its authority

for drug approval

and and as well as the compliance

activities right so the constitution

gives legislative

funds we have legislative function in

the constitution the executive and

judicials fda as you can see the

department of health and human services

comes under the executive functions and

food of food and drug administration is

within that

so

congress

they they institute the make laws right

so once the laws are there laws are very

very broad right so once the laws are

there the fda they will interpret the

laws and they will have regulations

there

and it will come in in the next slide so

they have regulations and then they

provide guidances to the sponsor so

lets see all of them just one or two

slides as a primer for all of them and

then they provide guidances actually so

that we will look at

how to do things

right thats what the guidances are

provided so so lets look at the laws so

the the relevant law some of the the

most

important ones the relevant ones these

are legislations passed by the united

states congress right those are the laws

for example the food drug and cosmetic

act of 90 all the drugs

you know have to be have to be safe and

purdue for prescription drugs use a fee

if you are developing your formulations

and then you are paying a fee for it and

so gdufa if you are developing a generic

drug product you are paying a fee for it

so these are so congress as well

you know for for example theres a

biosimilar user fee act of 0 so

congress says all right you know for a

bio similar product a protein or

biosimilar product charge a fee but what

kind of fee how to do that how much do

you charge and how much

so what kind of applications

and and how do you charge and those kind

of things they come in either

regulations or or guidances

so hatchman wax art

hatchboxman act uh made generic drugs

possible so these are

some of the laws that congress has right

so what does fda do with those laws no

so by the way that the proteins and the

biologics they come under in the public

health service act of so in this act

the biological product is defined as a

virus

a therapeutic serum a toxin antitoxin

vaccines come out of this blood the

blood component or derivative

allergenic product

applicable to the prevention treatment

or cure of a disease or condition of

human being you see these are very very

similar to the definition of drugs where

there is treatment cure mitigation

prevention of the disease right

so

the reason i want i wanted to mention

that was in fda theres a center here

the cedar that regulates

therapeutic proteins like enzymes and

other therapeutic proteins and

monoclonal antibodies

right but rest of the protein products

if they are used for

for for diseases

uh rest of the protein products they go

to sieber right so center for biological

evaluation research so if youre looking

for guidances for

monoclonal antibodies or therapeutic

proteins youre looking at cedar

guidances right for all other products

youre looking at receiver guidances

now

regulations these are rules

issued by fda these are consistent with

the laws right

and for example if you are really

looking at an ind investigational new

drug that cfr is where you look at

right if youre looking at a new drug

application then youre looking at cfr

bla is as i indicated to you

theres a phs act so if youre doing

human studies irb studies then cfr 0

right so those those are regulations

that you will look at

now

if we distill down further then there

are guidances so all right we are saying

that

uh

uh in in the previous slide we are

saying that failed inds you look at that

right but how exactly it needs to be

done what needs to be done and those

things are there in guidances so and

guidance by the way these are informal

documents right so they are

they are clarifying the requirements and

they are nonbinding but it gives a

pretty good information about the

development so for example if you are

developing a cyclosporine ophthalmic

product then theres a guidance for it

the last one here if youre looking at

immunogenicity of therapeutic protein

products now youre talking about

protein products right if you want to

look at immunogenicity how do you do

that for what kind of products you do

that with what frequency you do that

which models you use and those kind of

things you will look at this guidance

here from fda right so

so so now you know youve seen the laws

the regulations and the guidances so the

basic principle

for the mission the functioning of fda

is no drug can be marketed in the united

states until

substantial evidence of his quality

safety and effectiveness has been

provided to fda satisfaction

right in quality we are looking at the

characteristics of the drug including

its manufacturing so if you have protein

formulation right how youre looking at

the characterizations as well as its

manufacturing so they look at the

quality data they look at the safety

evaluations which is the relative risk

of harm and they look at effectiveness

and essentially theyre really looking

at

at the risk to benefit ratio the benefit

should always outweigh the risk you know

everything has risk right no matter what

you take

theres a risk right sometimes people

say that hey you know this problem has

this adverse event or this problem

this this this product has that problem

or this problem yeah problems might be

there or even the adverse events might

be there but the overall benefits

far far outweigh the risk then only the

product gets gets approved

okay

now

we are looking in fda really depending

on the nature of the product you are

developing it has different centers

right for example if you have food

or nutritional supplements or food

things youre looking at cifsan

and if you have a developing product for

veterinary medicine then you you have

cbm right if youre developing a device

containing some proteins then youre

looking at

cdr rage center guidance is right and if

you are if you are developing drugs or

therapeutics with proteins then youre

looking at cedar guidances and if youre

looking at some

proteins for example if youre looking

at looking at vaccines or our cell

therapy products or gene therapy

products are our blood related products

then youre looking at youre looking at

siever guidances right so same thing you

have tobacco center your national

center for toxicological research is

done in arkansas mostly and then the

compliance activities are regulated by

by fda

by by the office of regulatory affairs

so

so fda looks at the new product reviews

they look at safe manufacturing and

handling

they look at

provide standards and regulations they

also do research and enforcement

function so i wanted to provide

this little bit of background to you

so that you will have things in the

perspective when you are looking at your

discoveries and development of those

protein products so

fda reviews the results of laboratory

animal and human clinical testing done

by companies to determine

if the product they want to put on the

market is safe and effective right so

essentially a lot of

preclinical work the discovery work the

development work the manufacturing work

the scaleup work

uh the the clean farm work the clinical

pharmacology work as well as the

clinical studies

a lot of things are seen and only if

theyre satisfied the product gets

approved now also remember that fda does

not develop drugs all right

and so and this is not like a national

testing laboratory also so the testing

that is done is mostly in support of the

review function or sometimes its in

support of the field functions right but

its not like a testing

laboratory for anybody else to use

so they do the premarket review of new

human drugs and biologics complex

medical devices food and color additives

infant formulas animal drugs so this is

some some basic work that fda do now

this is an important slide it just shows

that

when a drug

is developed a protein is identified it

shows some function it

then these are the studies

uh for example the chemistry and

manufacturing so either you are

synthesizing the protein or or you are

you are deriving it

low molecular weights or the peptides

youre synthesizing or you are deriving

it from some cells or you are extracting

it from some other

place

mostly the from some organs or

different sources

so

so you have a protein there so youre

looking at the chemistry and the

manufacturing so you all know that a lot

of animal studies are done right these

are shortterm animal studies are done

and for chronic youre doing a longterm

animal studies are done so once these

things

are done you see this element here the

formulation development a lot of people

tend to miss this information i have

seen even the proposals that i see in

the study section in nih a lot of them

have a good information about this

very good information about animal

studies but this information a lot of

times is missing and because of the lack

of this information the products cannot

go to the ind so a lot of products get

killed here itself they dont go to ind

and even if they go to the preliminary

the

even if the ind is submitted then later

on youll have a problem during your

phase one or phase two or phase three

studies or in the pk studies but if you

want to cross the barrier from this

initial development and discovery we

really need to understand the ind very

well so that way we can focus our

studies

for some meaningful

development right so the formulation

development is an important aspect here

in this one and same thing once the ind

is done thats not the finished

formulation thats going commercially in

the market even if the formulation goes

in ind then therell be lot of changes

in that formulation depending on what

stage of the development it is so

eventually when all the studies are done

thats when the formulation gets logged

in the previous studies

the formulations you are changing

experience you are changing process you

are trying different things so you have

a lot of latitude in the development in

the initial studies but as you go down

further in different phases like phase

one and phase two and phase three and

and really at this stage here at the end

of phase two or phase three the the

formulations get logged in after that

you dont wanna make changes there in it

its very very difficult so the eventual

final clinical studies that are done

its done with a

with a

fixed formulation that that doesnt go

undergo changes there in it we will

learn more about it

so

if you

so this stage here in ind if you want to

go so this is

this is an important thing to know so if

you want to go for ind events to have

your discoveries what do you actually

need to

get into humans for testing right so so

really this thing needs to be understood

very well you see this

cmc chemistry and manufacturing control

this thing needs to be understood very

well you are able to reproduce it you

are able to test it you are able to

consistently obtain

obtain data thats consistent right so

its not like youre getting some peaks

in your mass spec on hplc and tomorrow

youre not getting that peak at all so

what is happening there is that because

there is no

results or is that because there is no

no drug it in it at all or something has

changed there completely right so we

need to understand this very well

chemistry and also what we are looking

at is a preclinical uh data with the

animal

obviously you saw that it is it it is

safe in a rodent species on a nonrodent

species so animal species you have done

uh some studies there in it so chemistry

and farm talk studies when theyre done

then we have we write a protocol for

administering the drug to humans and

thats when you get your uh you you

submit the ind to the fda because fda

when they are looking at it they want to

ensure that the medication if it goes to

human before it goes to humans you have

collected sufficient information so that

when it goes to humans then it is it is

it is safe to them its early part is is

mostly about safety right

and so so thats how the ind is

developed so if we really pay attention

to this uh cmc part attention to farm

talks but i have noticed that a lot of

attention is based to the farm talks

part

not much of attention is placed to the

cmc part and thats where a lot of the

discoveries

end up prematurely without even going

for the ints right now the ind we will

see some of them there are different

types of inds

so either it could be just investigator

ind you know investigator has done

something some work and then wants to

look at administering humans and test it

that will be an investigator id it could

be a commercial ind the intent is to

commercialize it move very fast uh

for example youre seeing the vaccines

now right so youre seeing a lot of

vaccines under development and some of

them are in emergency use authorization

theyre for commercial purposes even

though theyre in indias various

different phases but we already know

ahead of time that they are for

commercial purposes right so they are

traditional uh inds they are treatment

inds theyre exploratory inds theyre

parallel track inds theyre emergency

use inds so there are different types uh

we will we will look at some of them

that will that will tell you what kind

of uh studies and

that are needed and

attention needs to be paid in certain

things

so

so what do we

need to submit in an ind application

theres a form we fill it out has

table of contents uh statement and

general plan of what you want to do

what you want to do

investigators brochure and you know

the technical qualifications and

knowledge of the

sufficient protocols and how youre

administering right and all that and

then all the cmc data the farm talks

data that indicated to you previously

and previous human experience with that

if it is if it is available right to

provide any previous human experience or

you know sometimes the experience might

be in some other countries right you saw

some literature or you saw

other people working in this molecule or

a related molecule

uh then

published journals or any other

regulatory uh

bodies have looked at it provide that

information if its available

so so this is

a minimum expectation right and in the

farm talks data what are we providing

some preclinical studies data right to

demonstrate safety to demonstrate

efficacy

again preclinical is in the animal

models right so you are

you are doing it in two animal species

rodent species and a nonrodent species

thats what is required in most cases so

demonstrating safety and efficacy

potential toxicities and optimal dosing

then identification and quantification

sorry

the investigators you know so who are

the investigators what are their

uh qualification that needs to be that

needs to be

shown

uh statements regarding where and how

glp studies were performed what the

studies perform in a glp environment a

good laboratory practices environment

and all in other words theyre seeing

that is there a sufficient documentation

for repeatability and reproducibility

right and

and you know sometimes the amendments

can be made you know you submit an ind

then new information comes up and then

you you provide uh amendments to it

right

so so so we provided safety

pharmacokinetics and toxicity

information right and and depending on

the route of administration if its an

iv you provide some information for that

or a routes are providing some

information for

uh that you intend to use uh in your

studies in humans right

so now so

ind

there is phase one that is very initial

investigation right after you do your

experiments in in the preclinical

models youre just deciding to work on

humans so you have applied for an ind

and you wait for about 0 days for the

ind and then if you dont get a response

for rnd in 0 days from fda theres no

clinical hold that means you can move

forward and start your phase one studies

but if the if fda has questions or if

they want to put on whole this clinical

study then they will get back to you

within 0 days right so

phase one study is normally done in 0

to 0 subjects most of the time the

study is done in normal volunteers

unless its problematic for example in

oncology or

or

places where there could be some serious

adverse events

so you dont want to give those kind of

drugs to normal volunteers when they

dont even have the disease right but in

all other cases most other cases that

you use normal volunteers in phase

study right usually use anywhere from 0

to 0 subjects

youre looking at some of the admin

studies on that one very early safety

studies is what youre doing on phase

one study but if the phase one results

come out well then you know there are

the subjects are safe and you are able

to look at you know the absorption

distribution metabolism and an excretion

of that one

in normal volunteers if that data looks

good then you go to phase two

where you now you look at several

hundred subjects and these are patients

with disease understudy right so

youre looking at cardiovascular

condition so you are looking at patients

with that cardiovascular condition

youre working on a diabetic medication

youre looking at subjects who have

diabetes and so so usually these are

patients these are several hundred

subjects these are well controlled

uh so essentially these are safety

studies with some efficacy of safety and

efficacy studies

uh

and if the phase two studies also go

well then you go to phase three studies

here thats where you have lot of trials

here the randomized

uh

wellcontrolled studies what you need

here from hundreds to thousands of

subjects in multicenter in different

places these are very very elaborate

studies right so this is also for

patients with disease under study so

there are a lot of efficacy elements

here in this one of course safety is

there but you you focus a lot on the

efficacy of this one now once these

things are done usually nda is submitted

and nda

is is approved if they if the nda is

approved sometimes their commitment for

phase four studies post nda approval

studies right so sometimes there are

some risk evaluation mitigation that

they need to do or sometimes they need

to look at a product

after approval to ensure that it is

received well by the general population

where it might be going in millions of

patients right so phase four studies are

done so you got a glimpse of how ind

studies are done and another thing i

would like to suggest for especially

good scientists the basic scientists

you can have meetings with fda they

would love to see you they would love to

talk to you they will give you some

advice as to what kind of what kind of

studies you need to do and you can have

preind meeting as you can see here even

before you go to the ind

sometimes people dont utilize this

opportunity and then end up doing

studies

which are unnecessary which are

unnecessarily elaborate

elaborate study and so its good to have

meeting with fda and discuss say this is

what we have done so far what else do

you need and before you conduct those

studies its good to have a meeting so

there are different types of meeting

really theres called a type a meeting

where if youre already developing a

product theres a problem with that

product you want to meet them so this is

a type a meeting but most of the

development meeting that were talking

about today is there are type b meetings

either you can meet a preind or end of

phase one once you complete phase one

now the question becomes what kind of

patients whats inclusion exclusion

criteria for that one what kind of

endpoints were looking at or what kind

of doseranging studies that you might

be doing and those kind of things

you want to

have a

end of phase one meeting for that and so

do phase two studies you can do end of

phase two you can have a meeting there

pre

phase three meeting you can have end of

phase two meeting and the prephase

three meeting its usually called end of

phase to a meeting or end of phase to be

meaning

or you can have a prebla or prenda

meeting once you complete phase one

phase two phase three when youre

submitting the dossier its always good

to have a meeting there and and those

meetings will tell you what kind of uh

submission you need otherwise people

might give tons and tons and tons of

information some of them may not even be

useful to fda so its good to have a

meeting there right so this is the

process we go through for the

development and type c meeting theres

any other general meeting anything

outside of the development also you want

to go and talk to them uh theres type c

meeting there theres a form that you

fill it out and for that for that

information so its good to know that

there is an opportunity to go and talk

and see what kind of studies are needed

now

for for the ind there are different

types as i indicated to you uh uh

previously in one of the slides then

there is uh there are uh

so you can have an accelerated

development in the accelerated

development if you have

uh

lifethreatening illnesses then you can

have

uh

so there are two circumstances under

which the accelerated development and

one of it you are using a surrogate

endpoint uh rather than a direct

pharmacokinetic endpoint you can use a

surrogate endpoint for that right and

second thing when the fda determines

that the safe use of a product depends

on restricting its distribution or use

so

so

you need some some special population or

you really want to every for example i

can think of some of those some of those

opioid products or

are

some special disease conditions that you

use these products where

the the its its restricted from some

special population right

so

manufacturers must continue testing

after approval to demonstrate that the

drug indeed provides therapeutic benefit

to the patient right the advantage of

accelerated development review is the

review is done much faster

so these reviews are done a whole lot

faster

now the treatment inds the treatment

iron days you

are

looking at

any immediate life threatening disease

means a stage of a disease in which

there is a reasonable likelihood that

death will occur uh some of the examples

of advanced aids or hyper simplex

herpes simplex anticipators are

subarachnoid hemorrhage some conditions

where the treatment ind

essentially

this is often called a single patient

ind where

they are made available to patients

before general marketing begins right so

for example the product is there in a

phase three studies the product is not

approved

right

but you can give this to

a patient

right

otherwise the medication may not be

available to that patient

so

then then we will see the exploratory

ind in the exploratory ind

these allows quick human studies you

know you dont have to wait for all the

data youre just exploring so it is

conducted very early in phase one

and it involves very limited human

exposure

important thing is it has no therapeutic

or diagnostic intent you know sometimes

people may question right if theres no

therapeutic uh or diagnostic intent why

are we doing right so essentially the

product has not been developed yet the

product is actually

uh

you see the guidance does not

distinguish between a drug product and a

drug substance so you have a drug

substance which is a chemical and that

chemical gets translated to a drug

product right so here you know

so its not

distinguished between a drug substance

or a drug product so its a very early

on study thats why its saying that

theres no therapeutic diagnostic intent

because the formulation is not developed

at all right so there are

guidances given for explanatory

exploratory ind so dont just end up

doing a lot of work unnecessarily

because youre allowed to

explore very early on if you want to

administer the humans and test you can

do that by exploratory iid

parallel tract ind

under this policy patient with aids

whose conditions prevent them from

participating in control clinical trials

so you have a patient

who doesnt have a medication because

its not approved and they cannot

participate in a trial because you know

because of the inclusion and exclusion

criteria sometimes they get excluded

there so these are those kind of

patients and they can receive

investigational drugs uh shown in

preliminary studies to be promising so

if you have a promising drug

and

somebody wants to use it its not

approved and theyre not even a part of

the trial they want to use it so it does

allow

the policies do allow

the patients to get that medication

emergency ind

uh an emergency situation that does not

allow for an ind submission so even ind

is not even submitted and is not even

submitted right so

but there is an emergency situation

right

so fda allows

this allows fda to permit treatment of a

patient in advance of an ind submission

if something looks promising theres

nothing else theres no other

alternative its a its a its a serious

condition so

you can use emergency ind so

probation is provided

there are provisions for that study now

subpart e

there is

a section where

when there is no satisfactory

alternative exist then

you can give that medication so so a lot

of opportunities exist for giving drugs

to the patients in different forms of

inds i just thought of highlighting

those things now once it goes to the

submission after all the ind studies

this is for

this is what we need to pay attention as

we are developing as we are discovering

and developing the drugs so its not

like oh i knew this mechanism i knew

that mechanism you know that

thats not that important now though

because whats important is we know that

whats a medical officer is looking at

what the pharmacology folks are clinical

pharmacology you know the farm talks

folks are looking at what are the

chemistry people looking at what are the

biopharmaceutical

people looking at you know these are you

know drug dissolution and things like

that right

and then what is

the statistical folks looking at whats

microbiology so it has to pass the

scrutiny of all these these people here

right so once it pass then the review is

completed by the way once the reviews

are done sometimes there is a meeting

with the sponsor or sometimes theres an

advisory committee meeting you may have

seen recently for the vaccines right

every time the vaccine comes out whether

its a jj or modern or pfizer there are

advisory committee meetings to provide

recommendation its not done all the

time but its done sometimes right

thats why the committee opinions are

taken right so after review is done you

have a sponsor meeting advisory

committee meeting when the review is

completed if the review

is not acceptable sometimes there are

deficiencies major or minor deficiencies

so you go back and look at it and

provide additional information to fda

right

but if if this is completed review and

it is acceptable then you look at the

labeling if the information provided on

the label right

if

the labeling information if it is if it

is not good go back to the sponsor and

have them change the label right but if

the labeling is okay

and then it goes to inspection for the

site where it is manufactured and then

if everything looks all right if the

inspection is good then nda action

either approved or not approved right so

nda action is done if the inspection

side if there are issues there there is

pending satisfactory results right so

thats how the nda gets approved just

one thing that you know a standard

review time for an nda or a bla is

months but if it is submitted in

priority or accelerated development in

in the priority development then its a

six months time

uh

the the subpart age

accelerated approval based on surrogate

markers subpart eye this animal rule now

there are drugs that are approved in

conditions where human studies cannot be

done at all for like i remember one drug

prussian blue

when you know if theres a dirty bomb

uh if your radioactive decontamination

is needed right how do you do clinical

studies for those products right so

those some of those studies are done

so fda uses regulations and product

standards

right to approve the drug and then fba

uses the enforcement actions you know if

something doesnt go well if something

fails they need to correct all those

things then they can ask them for a

voluntary recall or they could be

injunction or seizures and things like

that and so that will give fda that so

fda has an enforcement authority

to do that so some challenges for

for for fda are the scientific

breakthroughs the pace of the work

especially the pace of the work in nih

and pace of the work and drug discovery

so much

then it takes a long time for fda to

catch up with that with that development

so so its its hard to keep up with

rapidly advancing technologies right

there are more and more sophisticated

products its unbelievable how

sophisticated the products are

and the new public health threats as

youre seeing now either antibiotic

resistant bacteria and now we are seeing

that you know the covet they have

different strains right now and you know

we are struggling to develop the vaccine

with a certain strain and now all of a

sudden the new strains start coming to

understand them to understand the

medications that are effective and and

making sure that they theyre safe and

effective and theyre constantly

reproducible what the drug we give today

should be same as the drug tomorrow or

day after until the expiration date it

should not change whether its a drug

protein drug or a vaccine or a gene

therapy product it should not change

right so these are these are challenges

that international

commerce and then the consumer

information you know people expect

this to know

so all those things

i think are huge challenges for fda

so we have we have seen that so there is

a discovery for the drug and then

theres analytical development and all

those studies are done and theres a

preclinical development its followed by

clinical development and marketing now

so you have a product right so if

theres oral product or a parental

product or a a lyophilized product you

have a product the studies do not end

here because after the product gets

approved you might want to make changes

there either you are changing a site or

you are changing some recipient or you

are changing some manufacturing method

or a process you want to improve the

process so thats why

we have to give annual reports for that

and there are different types of

supplements depending on the extent of

changes if the changes are not much if

theres a

annual report we have to give if there

are some minor changes then we have to

give supplements called cb 0 or 0 or

prior approval supplements then then the

post marketing surveillance is is done

then you do continuous

improvements of that product all that is

looked at right so theres a tremendous

burden on on the manufacturer i wanted

to tell you something that for the cmc

section if youre really looking at

guidances

then

for for monoclonal antibodies and

therapeutic proteins you look at cedar

guidances right for other proteins you

will look at the saber guidances so for

example you have office of blood

research in review so you will look at

some blood related blood products right

you will see the reviews there office of

cellular tissues and gene therapies they

have provided a guidance for cellular

tissues and gene therapies

you can go to this site and get the

guidance vaccine research and review

the reason they have separated guidances

are

the inds are highly

product dependent

for example the manufacturing scale

you can sometimes take a single lot of

product you prepared a lot of product

and you can treat thousands of patients

with that single law

or sometimes just for a single patient

you need multiple lots

right

some of the phage therapy ive seen i

was involved with one of the work where

i was amazed to see how

uh the

different phages were obtained and and

and sometimes the amounts like for

example the bioreactor the amounts

obtained are so low in a bioreactor you

have to combine several of those lots

and theres a process to do that to do

those initial studies right so sometimes

you need a lot of lots

just for a single patient so there are

different methods different technologies

different product characterizations

technologies right

practicality of testing its very

difficult to do a comprehensive testing

uh all the times right so thats why a

lot of things needs to be balanced out

to find out the risk versus the benefits

to the patient

now

the the risk so for example if a product

is there in the blood research and

review division right within the siever

coagulation factors are derived from

either human plasma or culture media

from genetically approved

engineered cells

for replacement therapy to treat

patients with congenital deficiencies

right these are these are blood products

so it has benefits right so we know the

benefits of the blood products right

they are effective in controlling

bleeding episodes

uh sometimes they could be

lifethreatening so these are blood

products that are reviews right so what

are the potential risks so when theyre

looking at inds and when theyre looking

at eventual approval some of the thing

infections due to adventitious agent

right so the way you are deriving

your your your

drug products so you are looking at they

may be adventitious agents so there may

be infections due to that or sometimes

theres a development of neutralizing

antibodies

right or sometimes theyre just allergic

impurities right so they will focus on

these things now if youre looking at

vaccine products for example

so these are combination vaccine

composed of bacterial antigens such as

toxoids or polysaccharide theyre

different types of vaccine this is just

one example here right so benefits

theyre highly effective to prevent as

well as treat or eliminate disease a lot

of diseases got eliminated completely

right

so

theyre theyre protecting healthy

health of vulnerable population right

and it can create a herd immunity a lot

of benefits of using vaccine products

right but there is two adverse reactions

are not detected early on the

immunogenicity issues the herd immunity

is dependent on immunization rate

and

decrease in risk tolerance with

declining disease if a disease is

declining the risk tolerance also

decreases right so those are some

challenges that theyre looking at and

which the sponsors need to address when

theyre developing uh protein products

or the vaccine products

now cell and gene therapy products if

these are autologous the stem cells

selected using monoclonal antibodies and

then they are expanded in a culture they

are matured with cytokines and then they

are giving back to patients you see the

process is much more involved right

unlike the previous ones so the benefit

they are very potent than current

therapies

they are applicable to wide range of

very difficult to treat diseases some of

the diseases are so rare

right so you can you can treat those

diseases they may have fewer side

effects there theres a lot of you know

theres a very targeted approach so

these are benefits but

it has a lot of risk in it right

potential for tumor geneticity there in

it

cellular contaminants there

the safety of the reagents

since so many of them are involved the

sterility of the product

uh

product tracking and segregation issues

the the characterization of these you

know the insufficient characterization

these are some of the problems of

the application that are submitted

product stability product variability so

a lot of those things so when you go to

this division of cell and gene therapy

products they are looking at all these

things right so depending on the office

depending on the product

now

now i will talk more about the

characterization and more focus on the

protein formulation

development for a scientist for example

if

this is a

this is a protein api so you are

developing for example a monoclonal

antibody

or are deriving it from cells right its

taking it out from a bioreactor

or youre so this is

just a drug substance youre not talking

about a drug product yet youre only

talking about a drug substance just the

drug substance the variability

or the problems can come from the way

you run the bioreactor you know it has a

lot of variables the cell variables

itself the feed variables right the

processing variables whats the stirring

speed we have done quite a bit of work

with

with bioreactors and im sorry i did not

list publications here there are a lot

of publications you know that uh

where we have looked at the variability

within the bioreactor theres tremendous

variability uh that that can come from a

bioreactor process and the way uh they

they can degrade and analytical methods

also right either youre using size

exclusion or youre using lc mass spec

or a gc gcms

or youre doing bio assets there so we

need to have good validations of these

methods there the environmental

conditions of i know one of the

monoclonal antibody we were working with

the buffer made such a big difference

right the activity

was

so different when on the sorry the

stability with one of the buffer we were

struggling that it kept changing and

then when we changed the buffer system

and it was

the protein was fairly stable so

so the environmental condition the

temperature the moisture the ph the

light the ionic strength buffer

concentration the dielectric constant if

it is a

a liquid formulation the protein

formulations right so

so all these things can make changes the

variability can come from

from that a degradation mechanism you

know you can have some aggregation there

you can have adsorption you can have big

glycosylation

you know so a lot of reactions can

happen there so thats why it requires a

thorough characterization studies

for

for

your primary structures for your

secondary structure for your tertiary

structures right a lot of those and the

association quaternary association we

need to have a thorough understanding

this is just

for getting the protein molecule and the

drug substance itself right

so some potential steps for example if

you are obtaining an opi right you you

have you have cell banks then you are

tying the while thawing can bring so we

need to have a good understanding and

documentation to show that this you are

getting consistent results inoculation

preparation right after youve

free star

then you have inoculation preparation

then youre running bioreactor you know

initially you might be running small

bioreactors then you might be running

large bioreactors right 00 liters 00

liters or even 000 liters or even more

uh bioreactors right and then you have

all this you know

liquid thats coming out centrifugation

and filtration downstream processing

there

and then you may have to run several

chromatographies there right for example

ligand chromatography or you may have to

look at metal helix there

then you have to do inactivation the

viral inactivation thats done at low ph

right

then youre doing ion exchange

chromatography then youre doing wild

filtration and then youre doing ultra

filtration

so you can imagine how many and then you

may have to run some reductive amination

or certain

reactions there right and that involves

after that it involves even more

chromatograph infiltration and then

there is a bottling and freezing

and then after all these things then you

are using so many different methods for

analytical characterization so its a

its a tremendously

burdensome

process

with a lot of potential for for

variability so unlike small molecules

where theres a lot of freedom for for

manufacturing a lot of uh

flexibility this has very little

flexibility because since the variables

are so many anything can make dramatic

changes there on this product thats why

its a very very restricted form of

development theory

so some critical quality

attributes

for the protein molecules

uh

whether its a peptide or protein

molecules appearance is very important

the osmolarity is seen thats what fda

is looking at all this information right

the ph of the product i indicated to you

the ph could you know have a very

significant effect on it on its safety

and efficacy and stability the primary

sequence and the peptide mapping for

identity then youre looking at protein

characterization

then the product related impurities the

process related impurity the host cell

protein the hostile dna etc and the

toxin or virus so we are looking at

process related impurities or you know

if there is any glycosylation profile or

you know there are carbohydrate

structure that needs to be characterized

then youre looking at secondary and

higher order structure you see the

amount of work that it takes for the

proteins now

now this aspect of the slide

people usually

the scientists do not pay a lot of

attention to it but its very very

important you know if your product

really has to see the light at the end

of the tunnel so you the previous slide

that i showed you was only the drug

substance the drug substance eventually

needs to a drug product because thats

what patient is taking your bla

or an nda or an ada

and das approved new drug application

so or a new drug application if its a

monoclonal antibody so if its a if its

a

cedar uh application

or

or

a b its a bla or india a nda all these

products now these products could be an

injection

injectable or it could be an oral

product or it could be a

subcutaneous product

injection or subcutaneous intramuscular

intra venous these are injections or

solid orals or

different types of dosage forms right so

previously we have seen drug substance

we have to go to drug product how do we

go there right so drug substance need

excipients you have to select the right

excipient

product properties the processing

condition

the environmental condition container

closure scale up dosage form all those

things needs to be looked at understood

very well to get the final product now

one of the thing i noticed in and some

of the academic scientists were working

on they use certain excipients and then

they do a lot of work on it and the

first question when you ask them why did

you use the excipient they did not have

a good answer for it oh we just tried to

solubilize it no when were using

excipient there are certain guidelines

for using excitement for example if the

excipients are well known no questions

asked we dont have to do a lot of

studies related to excipient

if the excipients are there uh in a

monograph like usp or some monograph or

fda has a database it publishes a list

of all the exceptions that are used in

concentration its available free on the

website you the excitement youre

selecting just look at the fda website

its called the iig

uh just just google it you will see it

so it shows the excitement has been used

if the exception is used in a certain

concentration for a certain route and if

you are using the same excitement you

dont have to do any any extra study

right

if theres a documented human use in the

proposed level

then you dont need to do any extra

study but if you have a totally new

recipient or if the excipient is not

there in the iit list you have a massive

amount of work that you need to do

theres a new excipient theres a

battery of tests you need to do just to

give you a flavor

i have shown

some of the

inactive ingredients guide right uh iig

lists

the amount

that is needed

and sorry ill keep in this slide

so the guidance

is a may 00 guidance it defines what a

new excipient means so if you have a new

excipient chances are if its not there

in the iig if its not there as a grass

if its not there in usp

chances are that it is the new excipient

if there is a new excipient these are

extra studies that people need to do

normally they dont do this studies

nobody wants to do these studies if its

not required right so but if we dont

know you develop something you progress

so much in your studies with an

excipient thats not characterized

a firm will have to end up doing all

these studies thats why they dont even

want to look at our discoveries because

the moment they see you use some

excipient

in all your studies

and and now

uh they have to justify they have to do

all these studies so thats why they

dont they dont even want to look at

those kind of formulation so you have to

do safety pharmacology studies if the

excipient is used for a short term the

disease is for a short term then the

acute toxicity day studies the admin

studies the genotalk studies one month

repeat those studies reproductive talk

studies all these things need to be done

if excipients are used if the

formulation is used for days of fuel

if it is used for two weeks to three

months

intermediate use

all the previous tests

but a threemonth repeat dose study but

if the excipient is used for more than

three months then we have to do all the

previous tests in addition to that

sixmonth repeat those toxicity and

other tests as recommended right and

then we have to do a twoyear

carcinogenicity test

right and for nonoral excipient there

are even other requirements so why do we

want to do all that right if you use the

excipient thats already used by another

uh

manufacturer ive already used in other

products or if its a grass recipient

you can avoid all these things so please

pay attention when you are doing even

your initial studies try to work with

exceptions that are well known

i just wanted to illustrate an example

so you have seen a product and then

sorry a chemical api when it goes to

process as i indicated to you there are

different processing or excipients or

environment or the packaging for the

formulation all those can bring

variability this is just one example

youre lyophilizing something right in

life realization sorry its not one one

one its one two and three three steps

uh you first freeze

the liquid preparation that we have by

the way when i look at life realization

one thing comes to my mind you know the

the covet vaccines that are there

uh the the physical vaccine it requires

uh deep freezing right 0 to 0

uh you know minus 0 to minus 0 then

you know the other one the

the moderna requires like minus 0

around 0 and then you know johnson and

johnson

refrigerator im just thinking that hey

you know what the c and c i dont think

they had time to spend a lot of

information on cmc they could easily

have been stabilized to run for a long

period of time and life realization

could be a great strategy to improve

their stability and increase their

increase their

ability to store at

lower temperatures and also

uh

increase their expiration dates

all right so so in freezing youre so in

lavalization if its a liquid product

you are freezing so theres ice crystals

and then your primary uh

drying so ice crystals are sublimated

right your sublime and remove the ice

crystal and the secondary drying where

the unfrozen water is removed right so

this is a life resistant process for

example ice nucleation here minus 0

degrees you are seeing this kind of eyes

you have if you have minus 0 to

degrees you have this kind of eyes and

so if youre doing the primary drawing

just one example i wanted to illustrate

because we spent quite a bit of time on

this one and published

quite a few papers on this one so if

youre doing this this drying

uh at this temperature if this is an

uncontro the freezing this is

uncontrolled ice nucleation you can

easily see this is the uncontrolled ice

nucleation here but if you have a

controlled ice nucleation

the your variability is tremendously

reduced

right this is beautiful

where

control when you have multiple vials in

a line of eliza so they are freezing at

different rates at different times

depending on the location of the vials

within the within the lyophilizer thats

why youre seeing this variability and

this one it just sublimes very quickly

in the controlled environment

so

uh

here is a formulation a monoclonal and a

body formulation that we had spent some

time on it inhouse just have it in a

bioreactor there and these are some of

the excipients we use to make a product

to do some of the

uh uncontrol and control experiment this

is an inhouse formulation

and the product was evaluated by hplc

uviz

uh dsctga and all those

uh different techniques the product was

evaluated i was just trying im just

trying to show you

the the advantage of control and control

thats the experiment we had done to see

uh the benefits now in the uncontrolled

if you see the specific surface area

this one the control one is much lower

the recon time the reconstitution time

is lower

uh the percent moisture

the

transition temperatures the particle

size so this is

a better

formulation and also the primary drying

time was considerably reduced right so

it just enhances the efficiency of

manufacturing

and also

the

the

the cake the liverization cake thats

obtained this was much better thats why

the recon time was lower in in control

so these are studies people can do to

enhance

uh then here we are just looking at

uh

and

control and and control some of the cd

spectra showing some data here so you

can get better i mean the process can be

enhanced still better this is just this

one study

so we had increased the process

efficiency

almost by 9

improve the quality

quality of the product by control

nucleation like that studies can be done

right now when we have the products

the expected characteristics for a

product i had shown you before in the

previous slide for the drug substance

now im showing you for drug product

right so appearance and color and

clarity identity the primary sequence

okay and the tests that are needed the

glycosylation profile the carbohydrate

structure the secondary and tertiary

structures the process related all these

things are expected to be submitted and

they will be looked at for

for

for the approval of these of these

protein products right so all these are

expected

uh

properties that are needed right in

addition to that characterization of the

product we also need to demonstrate the

stability data

right accelerated as well as the real

time right so there are conditions

either at

at

that there are different conditions for

that one right either i think degrees

and 0 humidity or 0 degrees and

humidity for certain liquid products but

in the case of protein products its

refrigerated conditions are are

very low temperatures right so

so even for stability samples the

appearance the ph the protein

concentration the purity with reverse

phase hplc or mass spec

are

are

impurities by size exclusion or specific

biological activity the endotoxin levels

the sterility all those things

are evaluated for

for the approval of a protein product

now very quickly the last a couple of

slides that i wanted to show you was

similar to the genetic product

for a for a small molecule you have a

brand product and a generic product

right so this thing is a biosimilar its

a definition of a biosimilar

biosimilarity so if if a pattern expires

for a brand product now you want to make

a

you dont call it a generic product here

you call it a biosimilar product here so

a new

uh provision came recently from the

affordable care act and that was the

original application for a protein

formulation is amphs the rld is

referenced a drug the brand product

right if you want to make a biosimilar

this is k right so biostimulator

biosimilarity is defined in section

or phs act to mean that a biological

product is highly similar this is the

requirement so its its almost

impossible to say it is the same as the

brand product because it is enormously

complex right youre talking about 0

0 000

uh molecular weight versus a small

molecule of 00 00 00 molecular weight

right and then a protein product you

have primary secondary tertiary

structures uh too many too many things

that can change in a protein thats why

its impossible to say

if the source is different that this

product is exactly same as the original

product so so the requirement is to show

that if they are highly similar

and if there are no clinically

meaningful differences

then you can get the product as a

biosimilar product or proof right so

so if you want to get a biosimilar

product what kind of characterization

theres a lot of physical chemical

characterization needed theres a lot of

biological characterization needed

preclinical work not much but it is

needed a lot of clean farm work is done

clinical pharmacology this is a this is

a

a course in clinical pharmacology so we

need to pay attention that for

for for a biosimilar a lot of clean farm

studies are done of course and

immunogenicity or some of the studies

are done not a whole lot

of of clinical study

uh after this but this should suffice

for the biosimilar so to give you an

example if you want to do clean firm

studies to demonstrate biosimilarity

some other we need to pay attention to

study designs the reference part of

characterization the study population

the dose selection the route of

administration the pk measures how do

you look at the peak images right its

not a small drug that you can just

analyze it its not very easy

the pd measures

defining the appropriate pd time

profiles statistical comparison of pk

and pd results and if there are any

extrapolations among indications right

all those things are looked at for the

for the bio similar product so its just

an example here for example you have

filgrastim right so you have so many

different if theres a cancer patient

with non myeloid

see this is the dose youre using

ive your subcutaneous so if you see the

label for field grasping it shows

that this is

a patient with severe chronic

neutropenia then this is the dose that

is used there right if the patient

is for

a bone marrow transplant

right

then

0 microgram per kilogram

is used for this one right

so

uh

so you have different

doses that are used

so thats why we need to do

some studies the clint farm studies for

that one

so

so when you have recombinant dna

products when you have monoclonal

antibody products

right so we need to

do

some clean farm studies

uh because the label has different doses

there in it so its just a small example

here

so

in a for a biosimilarity if we want to

obtain a biostimular for filgrastim or

for example another this is a

recombinant protein but you can do it

for a monoclonal antibody too so we have

to conduct pkpd similarity trials right

conduct safety trials right

uh so pk well characterized in healthy

subjects and patients similar pka after

you know

ivn

subcutaneous injection because that

product is used both for iv and

subcutaneous right because its done in

different doses different ways it is

used normally a product for oral use

youre comparing a small molecule with

oral use right but here you have

intramuscular in some conditions

subcutaneous and some other conditions

so we need to show under those

conditions theyre highly similar

so uh so

you you might be looking at some

neutropenia right

and so you are looking at them and then

comparing it you might be looking at

some of the biomarkers here you can or

you might be looking at some pd

endpoints cd for uh mobilization you

can you can be seeing it so those trials

you need to show similarity and then the

analytical characterization we are

showing that they are highly highly uh

similar there right

so

hopefully i provided you its just just

one class this is entire course by

itself so i just tried to condense all

that information

uh in in one presentation hopefully i

gave you a flavor of

the complexities of the protein and

things that you need to consider for

development just for both for the api

and what kind of characterizations you

need and then from the api then when

youre making a drug product then what

kind of characterizations you need and

what kind of you know stability

characterizations you would need and the

analytical characterizations you would

need hopefully i gave you a flavor of

those things and then i also provided

some regulatory

a background so that you can go and look

at appropriate

division

guidance documents so for example if you

are interested in pro vaccines you know

where to go and look at the cmc

requirement for the vaccines in of in

the division of you know ovrr in sieber

uh same thing for cell and gene therapy

now you know where to look at those

documents there and also you know that

excipients are are important early on to

select the right excipient because if

you use right except a lot of studies

that youve done

may not be of much relevance to the

industry thats why they dont take some

of our work very seriously right

so

i would like to thank uh

you know the fda staff ive worked in

fda for about and a half years as a

director and as brs scientist thats how

i got a lot of this information from fda

but but now im in academia so i still

do research and so i have post docs and

phd students that are contributing to

some of the work theyre doing

and some of the work i have done we have

done like a product recall its called a

pq factory product quality failure

assessment and control team they looked

at a lot of product recalls including

protein product recalls so we learned a

lot about why products fail sometimes

right so

the big team has helped me on that and

then throughout my my my my life are

both for the protein as well as the

nonprotein formulation science and the

clin farm work a lot of people have

supported the fda then i the department

of defense the texas state

as well as uh the university and the

pharma recipient sponsors so with that i

will stop here thank you very much im

sorry we are not seeing face to face

otherwise you know we would have had

some opportunity to do q a

but unfortunately i have to stop here

i wish you all the best and thank you

very much for for spending time with me

thank you

you