we are honored to have dr robert turner
currently a senior research advisor for
synthetic molecular design and
development at eli lilly
he has a responsibility for creating and
implementing drug product strategies
across lillys synthetic molecular drug
product portfolio dr turnick has over 0
years of experience in formulation and
development in manufacturing process
scale up and tech transfer
he has overseen the development of more
than 0 pivotal clinical and commercial
formulations
he sets on lillys pediatric steering
committee and is actively engaged in
both the us and european based
pediatric product development consortium
dr turnick is a pharmaceutical industry
representative on the federal task force
on research specific to pregnant women
and lactating women through hhs in nichd
please enjoy todays presentation
welcome to the nih principles of
clinical pharmacy course im dr robert

turnick senior advisor for eli lillian

company and its my pleasure to talk to

you today about drug formulation and

delivery

as disclosure i am an employee and

shareholder of eli lilly and company

so what is this lecture about today

today wed like to cover uh a number of

topics around the key patient technical

and business considerations when were

converting a drug substance into a

medicine with real focus on drug product

design and development

so the learning objectives for today are

um really around a review of some

principles of human centered design that

i find are really important in the

broader context of drug product design

and pharma

as well as critical quality attributes

um a short discussion on different

modalities

and then a lot of detail on some key

attributes of drug substance product

design drivers and routes of delivery

which will really form the the basis of

the talk and towards the end ill touch

very briefly on some pharmaceutical

packaging labeling and device

considerations as well as

a few thoughts on alternative

administration and special populations

so as you can see its quite an

ambitious agenda that we have to get

through today and so the real question

is is is where do we start and i think

it really starts with the patient and

this concept of design so why design we

can take lessons from orthogonal

industries like the food industry or

automotive industry where we see the

impact of of design every day and and in

the pharmaceutical industry you may ask

yourself well why would design be as

important when were not talking about

for example a consumer product and i

think a lot of the reason goes back to

just the evolution of health care in

society the autonomy that patients have

these days with regard to choice and and

dictating their own treatment as well as

the autonomy of physicians and health

care providers so choice does become a

matter of of a conscious decision

and so if we look at for example i have

on the the the image here around heinz

right you you think heinz sells ketchup

well they sell more than just the old

which in the glass bottle specialized in

maybe getting spots on shirts but as we

as we look at their evolution over the

course of time

they have a variety of products

available for for anyone that

wants to use ketchup whether they are

diabetic or whether they are on assault

restriction and and so these are our

simple illustration of the concept of

design and designing for a consumer and

their needs in their use scenario

so how do we bring some of that same

thinking into the pharma space is

something that im very interested in

and it really all starts with improving

um patient outcomes so we all know what

bad design can look like a porch on a

building with no access but what does

good design really look like

and how do we get there from a

pharmaceutical standpoint

a familiar example might be this little

package here that you might have run

into in a convenience store and it when

you have a headache and youre looking

to take your medicine

uh and then youve got to fold and twist

and pinch and tear and half the time the

the sloth is in the wrong spot then you

cant get the package open and and so a

poor design even if its something as

simple as as packaging for an

overthecounter pain reliever can be a

real source of frustration and so um

this is the type of thing that we want

to avoid as we think about product

development in the pharmaceutical

industry so where do we start we start

with the patient um and and this concept

of humancentered design and really

about building partnerships with key

stakeholders

patients themselves their caregivers

health care providers regulators and

even payers right and and and for me

its about keeping that patient those

therapeutic goals and their needs right

in front right front and center for the

scientists and the engineers that are

responsible for developing the product

and one nice way to do this is is really

by engaging in that conversation

being able to

understand build empathy through

understanding patient situations and

journeys and this is a place where even

though we may work as healthcare

providers or scientists were were all

people as well and we have our own

experiences in our in our personal lives

with regard to the healthcare system

and uh and those lessons learned and

experiences can be very impactful in the

way we think about the design of our

products as well so is this new to

medicine i i dont think it is and we

can go back

thousands of years and we can we can see

this quote from hippocrates that its

far more important to know what sort of

person has a disease than

to know what sort of disease a person

has and i think this really brings it

home uh in a very tangible way uh how do

you how do you understand your your

patient your customer so

with that as a background or some lead

in into the concept of design because

youll hear me use that word a lot

i want to talk about a few definitions

that well also uh frequently discuss

today

some terminology and and the main two

here are our drug substance and drug

product

so um the drug substance or the active

pharmaceutical our pharmaceutical

ingredient will use those terms

interchangeably um it it really is that

therapeutic um modality its that

substance thats intended to furnish the

pharmacologic activity um or affect the

diagnosis cure mitigation treatment or

prevention of disease that affects the

structure or function of the body and so

um

on converse uh or in addition weve got

the drug product which is really about

that finished dosage form and when i

talk about product i really am very

inclusive with regard to not just the

dosage form itself but also any

administration device or the packaging

or labeling that goes along with that as

well but thats typically thats that

final dosage form that tablet or capsule

injection

that is comprised of both that active

ingredient but as well its comprised of

a number of inactive ingredients that

are um that have an intended effect uh

in the performance of the drug product

as well

in addition to

those terminologies id like to

introduce the concept of critical

quality attribute and this is a physical

chemical biological or microbiological

property or characteristic that needs to

be controlled within a range or an

appropriate limit to ensure that the

product has the desired quality and

performance

both drug substance and drug products

have critical quality attributes and

theyre typically related to things like

purity biological activity release of

the drug

the bioavailability and the physical and

chemical stability of the product

some examples of critical quality

attributes might include impurities

in the drug substance or active

pharmaceutical ingredient

the solid state form

of the drug substance that we would

choose to put into a formulation

on a drug product side it might be

something like the disintegration time

for an oral dispersible tablet

if its slow if it doesnt disintegrate

rapidly when a patient puts it in their

mouth its not meeting the needs its

not living up to the design expectation

and so that becomes a critical quality

attribute similarly things like taste

for oral solutions

for pediatric applications sterility

for parenteral products of key

importance as far as a critical quality

attribute and even things like adhesion

of uh to the skin for a transdermal

patch are are nice examples of of what

we mean when we talk about cqas

those cqas are are

in many instances associated with a

particular specification for a product

but where we start in the design process

is the establishment of a quality target

product profile and what the quality

target product profile does is it forms

the basis of the design it establishes

some targets early in the development

process

that allow the scientist engineer to say

look if i can deliver against these then

i know that my product at the end of the

day is going to deliver the therapeutic

outcome that that we intend and so

concepts like

the intended use in the clinical setting

the route of administration the specific

dosage form itself

certainly the dosage strength or

strengths that need to be developed and

the flexibility

to provide

different dosing

over a diverse range of of the patient

population the container closure system

the release characteristics and well

spend a bit of time talking about that

later in in in the presentation um to

ensuring that the pharmacokinetic

characteristics the absorption of the

drug is really meeting the the

therapeutic goal and then as i mentioned

before those those

established quality criteria that from a

regulatory and a patient safety

standpoint we know that we need to

deliver against such as purity

stability for the product

so now i want to talk a little bit about

modalities and most of todays talk will

be focused on small molecules um they

are the most common uh type of drug

substance uh or therapeutic modality

that is on the market today and and

certainly historically these tend to be

small molecules small organic molecules

that are either synthetically created or

or natural sourced and purified um the

nice things about these small molecules

is that theyre stable theyre very pure

potent um and can be relatively

inexpensive to manufacture in contrast

with some of the other modalities well

talk about in just a second and and

similarly the small molecules will

support many m many routes of

administration whereas some of the other

newer modalities that are protein or

peptide based are fairly constrained

with regard to

the way that those drugs can be

formulated and delivered antibodies um

the first approved in the united states

in in 9 for an organ rejection

indication today

we see monoclonal antibodies um

advertised and marketed um across the

globe there are many many excellent

therapies theyre highly uh specific um

theyre very pure um the limitations are

are there as well theyre theyre more

difficult to formulate because of the

structure of the molecules themselves

and and really constrained primarily to

parenteral uh delivery the

peptide class of drugs is continues to

be an emerging class very similar in

some regards to the antibodies these are

all proteins if you will sequences of

amino acids peptides just tend to be

smaller sequences the two to fifty amino

acid uh sequence again primarily

parenteral delivery but i will mention

in the semiglutid example here that ive

got on the slide illustrates that there

is emerging technology thats been

developed and is continuing to be a keen

interest in uh in in the pharmaceutical

uh space around the delivery of of small

proteins or peptides orally um and the

drivers there are really around avoiding

uh

the need for injections it will help

with regard to convenience and

compliance for patients and

make the the great therapies that these

peptides have the potential to be more

accessible to more people

proteins um are obviously more complex

um large molecules d structure that

needs to be preserved to maintain their

biological activity um

present a real difficult formulation

challenge

um but but still we see um emerging

technology and more and more and more

products based on on proteins and then

certainly lastly i wanted to talk about

the car t s i rna gene therapies these

are new and emerging modalities where

the parental route is the primary route

or exclusive route of administration

and there are specific challenges to

these modalities which we wont get into

today but realize that as formulation

science it continues to evolve we really

need to um

be in a position where as these new

modalities are developed that the

formulation science and the ability to

deliver these specifically to the

intended site in a way that is

accessible to healthcare providers and

patients is going to be increasingly

important

so lets talk a little bit um

very quickly about just some of those

specific challenges which i ive talked

to

in the last slide or so um and im not

gonna go into a lot of detail here in

fact ill probably just let you read

through this slide yourself and say that

i know that in the uh curriculum for for

this course youll have opportunity to

learn more about the specific approaches

to formulating and delivering peptides

proteins in our and rnas but here you

can see a few of the key challenges that

the formulation scientists would need to

address

so lets talk about drug product and

well start with a very

familiar example from a synthetic or

small molecule standpoint and thats

acetaminophen if you look on the label

of the bottle

youll see that that drug substance that

active pharmaceutical ingredient

is acetaminophen

but yet we also see

a significantly long list of other

inactive ingredients what we refer to as

excipients

in that on that label in that product as

well um so that that

overall presentation the active

ingredient the

um the excipients and the formulation

uh com comprising the formulation along

with the package um and as i mentioned

in those instances if a device is

required and that label really

encompasses that entire definition of

drug product

so why do we create formulations and

there are a number of reasons both

patientfacing and and

from a manufacturing standpoint that we

look to

key are around enhancing bioavailability

potentially modifying or adjusting the

input rate of drug from the dosage form

into the patient

many times well formulate to help

improve the chemical stability of of a

molecule that may have the less than

desirable druggable properties

and then you can see some other drivers

here as well aiding in largescale

manufacture certainly things that would

be um more directed towards the patient

so for an oral uh liquid for pediatric

applications certainly taste becomes a

very important uh attribute and

something that we would

would look to develop a formulation but

through the use of excipients to uh

deliver a palatable formulation um but

it can also help with regard to safety

product identification allow for

blinding um of products during a

clinical trial um work and and also um

for example the use of preservatives to

maintain stability are all reasons why

we may

um

why we create formulations and you can

see just the variety of

of drug product types that ive got on

the slide here the particular

approach that we take and the materials

that we use to create those formulations

is going to be very diverse as well

depending upon the needs of the patient

the product

and our therapeutic outcome

so ive mentioned the word excipients a

number of times now and so just what are

excipients and these are materials that

are formulated alongside the active

ingredient of the medication that can

play a real functional role we talked

about some of these um particular uh

reasons why or reasons for inclusion of

excipients

i really think a key here is is keeping

it simple we dont want to add material

into a formulation unless we really need

that material and we also only want to

put it in there at a level

that is

that is sufficient to deliver the

functional purpose for that material in

the formulation in the first place we

dont want to expose

patients to any any more extraneous

material than what we need to the

excipients themselves by nature are very

inert these are all generally

generally regarded as safe materials

they have their own toxicology and

safety packages that associate with them

and so the inclusion of an excipient is

is typically

a very safe proposition but but

minimizing it keeping it as simple as

possible is uh

is a key thought process for a

formulator and to enable that we talk

about very early in development we we do

a lot of work on excipient compatibility

studies which are very critical studies

which can very rapidly narrow us down to

what are the proper excipients to use a

metaphor that a colleague of mine uses

frequently is is um you know going into

the chips ahoy the baking chocolate chip

cookie

uh metaphor where where you know if you

consider that the active ingredient is

the chocolate chip the excipients are

the flour and the sugar and the egg and

the vanilla and the other

uh and the other ingredients that go

into that cookie that actually carry

that chocolate chip um which we want the

uh um in the cookie and we want uh all

of our cookies to have a same or similar

number of chips um not no no chips in

one and a lot of chips and other and

this is really the the basic concept of

incorporating the active ingredient into

a formulation

along with the excipients

so

now were back to talking a little bit

about drug substance we talk about the

excipients the other components in the

formulation but obviously the key

component in any drug product is the

drug substance and i want to take a

little deeper dive into

those things that are are really very

important from a critical quality

attribute standpoint about the drug

substance that can ultimately affect

whats happening with the drug product

so recall those cqas and and what they

relate to um the purity the activity

the stability of the of the drug product

and and i really want to hone in on how

some of those drug substance critical

quality attributes kind of carry through

into um the critical quality attributes

of

the drug product itself

we talk about purity on the drug

substance and and um i dont want to

were not going to spend a lot of time

talking about the details here but i

think its important to understand

where these sources of impurities may

come from and why theyre there in these

synthetic molecules and so

um

the the synthetic schema right that is

typically employed in the manufacture of

a drug substance can be extremely

complex and well take a look at an

example in just a minute but the organic

impurities that come from

the starting materials the other

intermediates

things that may be degradation products

as a function of the reaction scheme

additional reagents or catalysts that
are used um salts that might be used in
the manufacturing process and another
really key class is is the solvents um
the solvents that are used all these
reactions take place in the solution
phase um those solvents um are very
critical in in the overall um
reaction schema for many apis and the
judicious use and removal of those
residual solvents is a key focus when it
comes to uh drug substance and and
impurity i want to call out specifically
mutagenic impurities which are dna
reactive substances that have the
potential um to interact with with the
dna and and can be mutant uh or
carcinogenic in their in their nature
this is a very special class of impurity
that we pay very very close attention
to as well
so lets talk a little bit about it
through an example
of of uh on vail sartan and this is
something that is um
been in the in the popular media over

the last couple of years and theres no

quiz im not going to ask you to

reproduce this synthetic scheme but what

i really want you to focus on is as the

number of steps in the reaction and then

particularly the reagents and conditions

that are listed in words below the

figure and you can see in there that

there are a number of acronyms number of

solvents dmf in this particular interest

ill draw ill draw your attention to

dimethylformamide

but you can see salts you can see

nitrates you can see

a number of different temperature and

time conditions that are that play in

here and so

when you think about the reaction schema

theres all kinds of opportunity for

side reactions um potential generation

of impurities and its essential that

the synthetic organic chemist really

understand each step of the of the

schema and have a control strategy in

place to um

to either reduce or eliminate any um any

side reactions or impurities that may

come through the schema

through the ich guidelines there are

very specific um impurity control

strategy requirements and specifications

we wont go into the detail here but i

think um again you can look at this

reference if you want to learn more

but its that these are very very low

thresholds um these these substances are

drug substances are extremely pure

right and tested to be such um and

theres good reason why why that is the

case um for the safety of our patients

what happens when we lose control of of

a reaction schema and it can happen it

has happened in the past in spite of our

best efforts and most recently over the

course of the last couple years you can

see the byline the date here january

09

a recall on medications additional

recalls on the same medication velsartan

that we were talking about and what

happens through the course of time um as

as more manufacturers

are producing the material were always

looking theyre always looking for

opportunities to

improve efficiency

um to save on cost and in this

particular instance the api supplier

altered a process

and contaminated the api with a

potential carcinogen this ndma nitroso

dimethylamine and ndea and nitroso

diethylamine which are known potential

carcinogens

simply through the introduction of

nitrates from

residual solvent and processed water at

very very low levels and yet it was

enough to spur an unknown or

unidentified at the time

side reaction which resulted in

the presence of these potential

carcinogens in the api

and what level are we really talking

about

down at the bottom line here

in in the instance of ndma and ndea the

fda put acceptable daily intake limits

of just

under um 9 and and nanograms per

day um from a quantitative standpoint

these are extremely low levels of of of

impurities in the system in in the um

api but yet at the same point in time

enough to trigger a recall from

the market

these same concepts around drug purity

um are in drug substance purity um hold

true for the biologicals as well i wont

go into the details here but

is as complex as the synthetic organic

schemas are

when were talking about the development

of monoclonal antibodies um or other

cellbased

drug substances you can see that the

opportunity for the creation of

adventitious viruses

fragments of host cell protein or dna um

molecular variants that would arise

during the manufacturing storage um

physical aggregation

aberrant glycosylation or deamidation

these are all things that when were

talking about making biologics can be

key

impurities of concern and so all these

same concepts that we talk about for

small molecule apply for those other

modalities as well

so continuing on with drug substance i

want to talk a little bit about now the

solid state the solid state chemical

form of the material that is the active

ingredient and the chemical and physical

stability of the drug product is largely

dictated by the solid state and form of

a drug substance and generally well

talk about this in

in two ways crystalline substances and

amorphous substances so crystalline

substances are those that have a a very

um welldefined molecular structure um

and ill give an example in a second

amorphous materials are those that its

the same molecular composition but yet

that that that that structure that

arrangement of atoms within that within

that material is very disordered and um

and and that can be an advantage and it

can be a disadvantage depending upon the

scenario

so why does solid state matter well i

mentioned that the those amorphous

materials um can be a blessing and a

curse and well talk a little bit about

that as we go through the the

presentation

generally amorphous materials are

higher they have a higher

solubility

and a higher dissolution rate and well

learn why that is very important um

later in the talk

but typically these are much less

chemically stable theres a lot more

molecular mobility in a more an

amorphous um solid um and and that would

lead to a greater reactivity in certain

environments and situations they tend to

be very hygroscopic they want to pick up

water and youll see in a minute that

water is an extremely important player

in the stability of amorphous materials

and they tend to be thermodynamically

unstable what what an amorphous material

wants to do is go to a more

thermodynamically stable form a

crystalline form and so if you start

with an amorphous material typically

over time that will want to become a

crystalline material the rate at which

and the conditions of which that will

happen can be vary

tremendously and in fact we can create

amorphous stable

materials but generally um it is a less

thermodynamically stable state and then

crystalline salts and polymorphs um

is is the other i guess major category

that well talk about here it could be a

freebase it could be a salt and within

that crystalline structure um we can

have different

crystal arrangements or different

atomic arrangements of those molecules

and and that will give us very different

physical properties from solubility to

melting point or dissolution rate and

physical characteristics of the solid

material as well and these attributes

can really affect the stability the

bioavailability and the

manufacturability of our drug products

so

making sure that were starting with the

desired form and staying with the

desired form throughout the the um the

drug substance manufacturer and the drug

product manufacturer and the stability

and inuse period is of critical

importance

heres an example of chemical stability

impact based on an aim or same molecule

but an amorphous napa disolate salt

versus the crystalline freebase and if

you just draw your attention to that

bottom boxes in in red youll see and i

mentioned the importance of water at

those elevated temperatures of 0 and 0

degrees in the presence of water

percent relative humidity um you can

see that the amorphous material um

degrades very rapidly less than 0 of

the drug substance left after a day

period as opposed to

the crystalline freebase which even at

those conditions of 0 and 0 degrees c

with a high moisture content in the
environment they maintain their chemical
stability and this is a really important
attribute in ensuring that you dont
have uh amorphous material in the
instance that youre working to
deliver a crystalline material and how
its important to stabilize an amorphous
material if youre going to use that as
your drug substance
so polymorphs will talk a little bit
more here on the crystalline side i i
mentioned that you know can be the same
chemical
composition but yet those molecules or
those atoms just arranged in a different
way and a classic example is graphite in
diamond right its carbon and in one
instance depending upon the way that
those atoms those carbon atoms associate
with one another we have graphite
and in the other instance
just by simply changing the way that
those um carbon atoms interact with one
another and the structure that theyre
in we end up with diamond and we can all

appreciate the very different physical

and chemical properties of of graphite

and diamond

so

what can uh the difference between a

salt or a crystalline structure or a

polymorph mean with regard to the

property of bioavailability the ability

of the drug to

get into the body and have the desired

therapeutic effect and this is a

just a simple example of a molecule that

was developed in my organization a

number of years ago where we looked at

both a hydrochloride salt form and a

mesolate salt form methane sulfonic acid

salt form and and in an in vivo

study we were able to in beagle dogs we

were able to look at the difference

between the performance of those two

um

salts of that same molecule and you can

see here in this instance that there was

almost a threefold increase in exposure

just based on

the different counter ion the different

salt that we used and so this is a nice

example of how

the solid state and form can affect the

performance of a drug product

what happens when we lose control of

that form another example here this one

from 99 um with the norvir or

retonavir product that was an age drug

still is that is used and um

surprisingly in in the middle of 99

several lots of the

norvier product failed the companys

internal um

quality control dissolution test um

which brought production to a halt

and really interrupted the supply of

this at the time very lifesaving and

critical medicine

so whats the story behind that um as

you can imagine it goes back to the drug

substance it goes back to form

at the time of the issue there were over

0 lots of norvir that had been

successfully manufactured but in the

investigation around these dissolution

failures it was determined that there

was a new

unanticipated crystal form that had

shown up in

um in the drug substance that was um

being used to formulate the capsules and

that this new polymorph had a

significantly lower solubility relative

to the desired form and the consequence

of that was not only a dissolution

failure but it significantly reduced the

bioavailability to only five percent of

the intended product um bioavailability

and and basically the product would be

ineffective for achieving its

therapeutic goal so a nice example of

how the um the drug substance and form

can um

and the control of that needs to be

maintained to ensure product quality

so now weve talked a lot about drug

substance and some key attributes well

come back to formulation a little bit

here and i really want to focus on a

couple of of these why do we create

formulation

bullets highlighted in red around

enhancing bioavailability modifying the

rate of drug input

well talk a little bit less about

chemical stability but

but well talk well mention that

briefly as well and so um

what are those overall product design

considerations around

why we formulate when we formulate and

certainly as ive already discussed we

need to understand the physical chemical

properties of the drug

but in addition to that we also want to

really make sure that were paying

attention to what our therapeutic goals

are and this can be very impactful in

the choice of the treatments that we or

the way that we would formulate

a drug and the type of drug product that

we will ultimately develop so if this is

for an acute treatment like pain or

migraine we might take a different

approach than if it was for a chronic

treatment for example high blood

pressure or high cholesterol um we also

think very hard about whats where is

the target whats the desired effect is

it systemic is it local whats the site

of action and through this we think

about um designing for that in vivo

performance around these bio what ill

call biopharmaceutical considerations um

and

excuse me im really going to focus on

the

the two the two pieces of solubility and

permeability um but certainly also we

dont want to lose sight of the patient

and the use scenario so as i mentioned

um product design considerations and

what were trying to achieve through our

therapeutic goals is a very important

consideration and can dictate where

were at with regard to the

decisionmaking process and the choice

of route of delivery

so as i mentioned earlier not all

drugs are able to be delivered by all

routes of delivery

and in fact even on the small molecule

side um it would be a very unusual

circumstance when the uh a given a

treatment or a given molecule was able

to be delivered through

this wide variety of routes of delivery

but i want to introduce these concepts

here as well talk about those more as

we advance through

the presentation

the

the route of delivery

is an important consideration and one

thing that we we talk about is kind of

whats that therapeutic need and time to

onset so if if this is an acute setting

um an emergent setting um and we need a

very very rapid onset of action this is

you know uh the the

the standard the gold standard with

regard to onset of action would be an

intravenous type of an injection its

immediately bioavailable in the system

um and can get to the intended site of

action and have the desired effect um

other parenteral

routes of delivery like intramuscular

injection a subcutaneous injection

and even an oral buccal tablet or a

nasal or or

pulmonary inhalation can have a very

rapid onset of action as well

tablets in capsules and particularly

modified release tablets tend to be more

on the order of minutes to hours to

achieve their therapeutic effect and

modified release or enteric coated or

coated tablets delayed release tablets

can

can delay the uh

the effect

onset of effect

for several hours

after the time of administration and

then also when we think about depot

injections or implants we can have a you

know long time before we see days to

even weeks before we see full onset of

action um and of course the duration of

action for those types of dosage forms

can be quite extended as well

um

another

important consideration from a

patientfacing standpoint is is really

um kind of preferred routes of delivery

and this is a a snapshot from i think

09 march from pharmaceutical and

really what it does is it illustrates um

the the products that are on the market

approved products or products that are

in the development and pipeline and the

route of administration um that that

they are using and so you can see here

that by far

um oral administration and injection

administration is are

the leader by far with regard to the

frequency of of route of administration

although inhalations ophthalmic topical

uh other um are not insignificant and

really very useful for certain specific

indications and treatments as well talk

about

in a few minutes

so i really want to bring us back to

talking to small molecule and the oral

route of delivery and this concept of

biopharmaceutics because i think this is

really important to understand and and

still forms a a large basis of uh

of of the discussion in the

decisionmaking process

for a formulation scientist for small

molecules um and really the key here is

is to just think about the gi tract if

you will as as a as a tube as a cylinder

right and and as we think about key

parameters of moving a drug through that

cylinder with the ability to

get it out of that cylinder absorbed

into the rest of the body some of the

key parameters are whats the total dose

that we need to deliver

the solubility of the drug in that

environment the permeability of the drug

the ability for it to go through the

tissues into the bloodstream to have the

desired effect

um the volume of material um or or

liquid in the gi tract and the time that

it takes for that material to go through

that tube are all

uh key elements and considerations and

kind of form the basis at a high level

for this concept of biopharmaceutics

from an oral delivery standpoint

so we come back to this notion how much

drug can be absorbed and

we use an equation its a very simple

equation to try to estimate or

anticipate what the maximum absorbable

dose would be for a given drug and it

really breaks down into a series of of

three constants an absorption rate

constant and some assumptions based on

small intestinal volume small intestine

focus because this is really where the

greatest surface area for absorption

exists within the gi tract

and where most absorption whether it be

food or or pharmaceuticals occurs

and then that transit time through that

portion of the gi tract that small

intestine and for the case

these examples well well talk about a

four and a half hour or so window um and

so really the the variable then becomes

this concept of of solubility right now

permeability also is involved in that

absorption rate constant and and well

talk about that as well thats we can

make some estimates or establish what

that permeability absorption rate

constant is and so really it becomes a a

question of solubility in the

physiological environment

to simplify this a little bit in 99

gordon avedon up at the university of

michigan and coauthors published

a paper um a biopharmaceutics

classification system and this is a a

foundational uh piece of literature and

a concept thats based on risk that

really provides a lot of guidance to

formulation scientists for how to

formulate drugs

and

as i mentioned it really is a riskbased

system and you can see

from a prior conversation if youve got

a drug thats highly soluble if youve

got a drug that is highly permeable

theyre really very low risk and we call

these bcs class molecules and it gives

us a lot of flexibility if our api has

those properties our drug substance has

those high solubility and permeability

properties the formulation approach that

we take i wont say that it doesnt

matter it does matter from a patient and

a quality standpoint but from a a drug

absorption standpoint it probably has

very little impact so for a bcs class

molecule if i

made it as a tablet or a capsule or an

oral liquid it probably would not affect

substantially the rate and extent of

absorption of the drug however for a bcs

class molecule that has very low

solubility very low permeability

relative to the amount of drug that we

need to deliver you could put that drug

into the gi tract and it will just pass

through with almost no drug being

absorbed and just excrete it out um with

the feces and so the bottom line here is

is we we break our drug substances down

into this binary high solubility low

solubility high permeability low

permeability it has significance from a

regulatory standpoint um and and its

adopted and embraced by regulators

around the globe in the us in

particular

and it really forms a nice way for us to

talk about

biopharmaceutics going forward

so when we talk about designing for

invivo performance then to getting the

drug out of the

gut into the systemic circulation we use

this noise whitney

equation as kind of a foundational

equation and im going to just simplify

this if i can by saying um the amount of

material the mass m that can be

delivered as a function of time really

breaks down into two key

attributes its the surface area for

dissolution of the drug

times its saturation solubility now in

this instance um the rigorous noise

whitney equation we talk about the

concentration of the drug at the surface

of a dissolving particle

versus the concentration c sub b

of the concentration of the drug in the

bulk um of the media or solution around

that drug but if we can make an

assumption that the that the

concentration at the surface of a

particle is effectively the saturation

solubility of that drug substance and

that c sub b the concentration in the

bulk is effectively zero because that

drug is being absorbed into the body we

can simplify this equation down and

really talk about

abilities to enhance absorption

and bioavailability through either a

increasing the dissolution rate

of the drug through surface area

increase or

by creating a kinetically stable higher

saturated solution of the drug in the

intestine

so we talk about this in terms of how do

you increase surface area well its very

simple its all about particle size for

drug substances we can micronize the

material even nano size the material and

get it into a very small particle size

with a very high surface for dissolution

and that can really improve the

dissolution rate in vivo of a drug and

substantially improve and increase the

bioavailability this is a very common

approach thats taken

in in pharmaceutics the other approach

um to increasing that that concentration

is through

presenting the drug in a way that is

more easily dissolved or in as a higher

soluble

state now we talked about salt

previously um and showed an example

about when we used a hydrochloride salt

versus a mesolate salt

in this instance id like to talk a

little bit about creating a solid

dispersion so if you go back and recall

what we talked about on the api about

amorphous materials we talked about them

naturally having a higher solubility

increased molecular mobility but we

talked about the risk of what happens

when you dont control that well theres

an opportunity if we can control it and

through the judicious use of technology

and excipients well talk about in this

instance a spray dried dispersion where

were intentionally creating amorphous

solid material that will have a

kinetically higher solubility and

dissolution rate with the intent of

delivering more drug through the

intestinal wall and getting us to the

concentration and therapeutic effect

that we need

so designing for in vivo performance

then well talk about this example of of

zelbarath it was originally improv

approved in december 0 for metastatic

melanoma for patients with a specific b

raf v00e mutation and similarly a

reapproved or approved with additional

indication on this uh on erdheim chester

disease of a very rare disease with that

same b rath mutation but if you look at

the solubility of this drug going back

to

you know what we were talking about

our assumptions um

youd

for practical purposes need a swimming

pool full of liquid to be able to

dissolve the therapeutic dose of this

drug and since most of us arent

accommodated to drinking quite that much

fluid

we knew that we really needed to do

something to

enhance the amount of drug in solution

and in the gut to allow for um effective

therapeutic concentration in the initial

phase one studies for this molecule the

sponsor chose to take the first approach

increase a and were very aggressive

with regard to micronizing the drug

substance but yet still an unacceptably

low and highly variable

bioavailability in those early clinical

studies

subsequently theyve reformulated the

drug substance as a solid dispersion and

a ratio of three parts drug to seven

parts of a polymer called hydroxypropyl

methyl cellulose acetate succinate

which created this solid uh stable

amorphous dispersion

that was able to be dosed

and we saw a five percent they saw a

five percent increase in exposure

much reduced variability and now this

drug is able to

be a

a high quality consistently performing

marketed drug through the use of a

stable

amorphous solid dispersion

so well talk a little bit now about

designing for invivo performance we

talked about this notion of achieving a

target plasma concentration or how much

drug we can get into the body

and this graph here on the right just

simply shows

a couple concepts with regard to

the release profile of the drug out of

the dosage form

and how that might affect the ability to

keep

a patient in the therapeutic range

potentially

extend the the duration of

time in that range and reduce the dosing

frequency and it can also provide a lot

of benefit

for narrow therapeutic index drugs if

were dealing with peak to trough issues

um keeping patients below

a toxic or

nontolerable range and yet preventing

them from dropping below into a

subtherapeutic range through some

technology and formulation and so i

really like to take a little time to

talk through some of this

the key here then is we talk about

modifying that release as opposed to

ingesting the drug and the drug is

immediately made available to

the the gi tract for

dissolution and absorption were going

to control the release of the drug out

of the dosage form to achieve that

therapeutic effect that we want and why

do we do this um i mentioned a couple of

the reasons

on the previous slide but to reiterate

it can really improve overall efficacy

it has the ability to reduce side

effects by controlling peak and trough

levels

plasma concentration

it could provide an opportunity to take

a drug that needs to be administered

twice or three or four times a day and

turn that into something that might only

be needed to be administered once a day

which will help improve on patient

compliance and give us a the therapeutic

outcome we want and it can also be used

along those lines for some competitive

differentiation modified release can be

used for multiple types of of

routes of delivery so it can be oral it

could be parenteral well even see an

ocular example

and for topical products as well

the um

typically this is used for

synthetic molecules um the technology

around uh delivery of biologics through

uh sustained action typically doesnt

happen through the formulation approach

a lot of times thats engineered into

the molecule itself

we wont get into that dialogue in this

talk today but i think youll have some

exposure to that in

either previous or upcoming

modules in the course

so id like to spend a little bit of

time talking about particularly

sustained release but ive listed out

the different types ive shown an

example here with uh

aspirin milligram aspirin that many

many folks take um

its a cardio cardiovascular protecting

but we know that the the acetylsalic

acid in the uh in the product itself can

at times create gi upset for patients

and so you simply put a enteric coating

which prevents that drug from going into

solution in the stomach relieves the

potential risk for indigestion or

or

acidosis in the stomach

and um provides a much much better uh

patient experience and thats just

through the use of a polymer to prevent

the drug from going uh into solution in

the stomach

so lets talk about a couple of

different modified release technologies

um that are very common commonly used

the first ill talk about is a

hydrophilic matrix tablet where the drug

is mixed with excipients um that

actually are hydrophilic uh polymers

that will will hydrate and swell

um and and as that

product hits the um the the gastric

contents the drug will be or the the

tablet will begin to absorb water it

will begin to swell um and it will

create a viscous gel layer around the

outside of the dry core of the tablet

outside hydrates quickly

and creates almost like a gel coat

around the tablet and then the drug

slowly diffuses through that that gel

coat in addition that that gel coat as

it hydrates great more water and and the

viscosity will drop at the surface that

that gel layer will erode and so the

tablet will will become smaller and

smaller but the drug release occurs over

a period of time and we can manipulate

those polymers

to really dial in how fast we want that

drug to release or how long we want that

tablet to stay intact

a similar technology is a reservoir

controlled release technology whereas

opposed to a polymer that will swell in

a road well put a film on the surface

of the tablet uh a polymer a

semipermeable membrane and water will

ingress into that

through that membrane it will solubilize

the drug within that

membrane and then slowly over time the

dissolved drug substance will will be

able to leach out through that that

membrane and

create a sustained release effect so a

couple of very common modified release

technologies i wanted to to share

but there are potential risks and

disadvantages with regard to modified

release typically what were doing in

those instances is putting

multiple doses of product

of the drug substance into a single

product with the intent that that will

play out over an extended period of time

and so the actual

drug load or amount of drug in those

extended release formulations tends to

be greater than if it was

an immediate release product for

um administration

and and so the risk there then becomes

is what happens if the dosage form fails

and all of that drug uh releases into

the system at the same time and that can

be a failure of the of the dosage form

itself if its not well designed and

controlled or it can be as a result of

extraneous effect or an intentional

effect so we talk frequently

particularly around

the hydrophilic matrices around

alcoholinduced dose dumping um so when

patients um they

they may continue

alcohol consumption even though um not

recommended in many instances when were

taking a medication um in this instance

the the data here by leonardness at all

led to uh the withdrawal of a product

paladon xl which was a hydromorphone

sustain release product

from the market because

excuse me of

the dose dumping potential in relation

to alcohol and um some adverse events

serious adverse events that had occurred

um and then i talked about the

intentional misuse of products as well

and were all familiar with the

um the crisis in the united states with

regard to abuse potential and and

opioids but other therapies as well

methylphenidate is an example and well

talk a little bit about that

but formulation science can also provide

a deterrent and so courtesy of pfizer i

can share this um

uh image right of their embedda morphine

sulfate naltrexone combination product

and really the whole driver here

is um to avert or minimize the the

the um abuse potential of this drug

through uh technology that um allows for

the morphine sulfate to be released

through a rate controlling membrane if

you remember the reservoir

design that we talked about before

but yet in the core of this um

pellet as you can see that its a

capsule thats comprised of multiple

pellets

theres naltrexone in that core so if a

patient were to take and open that

capsule and try to crush those beads

and release all the drug immediately

to get high or to have that um that that

that high therapeutic concentration of

of uh

of morphine sulfate it will release the

naltrexone and that will avert a serious

adverse event with regard to overdose

on the methylphenidate example i wanted

to share a unique technology allza

corporation developed this a number of

years ago for and is being used in the

commercial concerta product

and in this instance you have an

immediate release component of drug

overcoat on the outside of the dosage

form which releases the drug very

rapidly but then

there is a semipermeable membrane

around a threecomponent system within

that tablet

a cap i guess i should call it a capsule

shaped tablet and what happens is that

water will ingress through that

semipermeable membrane it will hydrate

the push compartment

solubilize

the drug in the drug compartment drug

compartment and through a laser

drilled hole at the end osmotic pressure

builds up inside that film and it will

push slowly push uh additional drug

outside

into the gastric contents for absorption

as a function of time and so basically

it takes a three time a day

methylphenidate dose and provides an

effectively equivalent therapeutic

concentration without the peaks and

valleys that you would see

if you can take a look at the plasma

profile concentrations from the concerta

package insert and provides a more

convenient and more um therapeutically

constant delivery of methylphenidate

so um

back to

some broader considerations on on route

of delivery what id like to do now is

is finish by going through

um kind of a survey of of different

routes and why we would use them

advantages and disadvantages um for

those different

approaches so we talked a lot about oral

formulations today and for good reason

they are

the most common formulations that are on

the market across

synthetic molecules today um there are a

lot of advantages to to immediate

release ir tablets and capsules theyre

very dose accurate theyre stable

theyre portable familiar to patients

theyre easy to identify from a safety

standpoint they have a relatively low

cost of manufacture and while they do

have some limitations those limitations

are are fairly minor um again theres

only so much drug that you can get into

a tablet or a capsule that is able to

easily be swallowed by a patient um they

do run the risks we talked about before

about pill crushing pill splitting dose

splitting um we see that as a

you know a potential disadvantage to

this type of dosage form but by and

large this is a very common very

effective way to

deliver drugs orally

we talked a lot about modified release

tablets and some of the advantages and

disadvantages

around that so i wont go into a lot of

detail here

just to remember that

from a manufacturing and a quality

standpoint a lot of times these dosage

forms require some specialized

excipients some specialized technology

um and so um and and not every drug is

really amenable to this type of uh uh

approach and so it does take a certain

circumstance a set of physical chemical

characteristics and therapeutic need um

to um to go the route of a modified

release but is a very common technology

nonetheless and something that a

formulator can look to

leverage to improve outcomes

other oral uh routes um

orally disintegrating tablets are a

popular dosage form um that we see

more and more frequently and

particularly

in space like migraine

where acute relief is

of primary importance to the patient

like standard dosage forms these are

dose accurate theyre stable although

physically robust the physical

robustness tends to be a little less for

the odts

a little more difficult to handle a

little less robust sometimes they

require physical

support through packaging

as opposed to a multicount bottle we

may use a blister pack

but they can be discreet theyre

portable

in many instances no need to take with

water

and theres a perception of onset of

speed with this dosage form that

that many patients experience as well

even though at times that may not be

supported by the pharmacokinetic data

it is a reality

i want to draw a specific distinction

between oral disintegrating tablets and

buckle or lingual tablets because

theyre not the same

while the buccal sublingual dosage form

will dissolve in the oral

cavity the the drug substance um is

absorbed through the oral mucosa with a

buccal or a sublingual tablet thats

designed for systemic action as opposed

to the orally disintegrating tablet

which is really just to disperse quickly

and then be swallowed with the saliva

and absorb through the gi tract so

buccal and sublingual tablets are fairly

uncommon and they really require a

molecule to be

to be designed to support that route of

administration i use the nitrostat

example here were familiar with that

its a very low molecular weight um drug

thats absorbed very rapidly through the

oral mucosa and can give her and can

give a very rapid onset of uh of action

um we also um can use buccal or

sublingual dosage forms for for local

delivery um for treatment um just within

the the oral cavity itself and in those

instances then absorption of the drug um

into the systemic circulation is really

not a consideration

um

rounding out oral formulations we talk

about oral thin films its kind of a

niche emerging uh dosage form um can

have some advantages for certain

indications

similar to the odt oral dispersible

tablet in many regards

discrete

the nice thing about the

odts and the fin films are that for

certain psychiatric indications

it can really avoid

cheeking of the dosage form so if the

patient takes the dosage form into the

mouth it really ensures that they will

get the drug

as opposed to cheeking a tablet and then

you know when the nurse walks away in an

institutional setting spitting it out um

and avoiding their therapy and then of

course oral liquids

play a role um for

many patient populations with regard to

an oral formulation just in a different

form

the nice things about oral liquids is it

really provides a lot of dosing

flexibility um and can

be a great dosage form for patients that

have a difficulty swallowing a solid

oral dosage form some disadvantages are

around taste um and and and really the

the dosing device and dosing error um

and ill talk a little bit more about

that at the very end

but its very important that these

products are designed and provided

with

the appropriate dosing device thats

well designed to avoid

dosing errors because in many instances

these products are actually being

measured or dosed by the patient or a

caregiver themselves and the risk is is

is high

and then of course there are additional

physical chemical and microbiological

attributes of

oral liquids that need to be taken into

consideration as well

theres some sprays lozenges gums

granules we wont talk about those but

each of these has its specific

advantages and limitations and depending

upon the disease state the patient

population and the desired therapeutic

outcome

can be very useful formulation

approaches

a little bit on parenteral

formulations and some key

quality attributes here i want to talk

through

really around sterility

microbiological endotoxin stability

particulate matter

sterility excuse me

very key critical quality attribute

considerations here

sterilization methods for parental

formulations um you can see on the top

right

a number filtration is is really a very

common and effective approach to take

heat a little less because the drug

itself would need to be unstable through

the heat cycle and we know that

heat can

really create problems from a chemical

or even a physical stability standpoint

um gas and

ethylene oxide and radiation are also

alternative um

sterilization methods that can be looked

at in the abs in the instance that

filtration

or heat may not be applicable um

we

additional considerations on chemical

and physical stability and interactions

with the packaging we call extractables

and leachables are our really important

attributes with regard to parental

formulation as well as the formulation

composition itself the isotonicity the

ph the volume to administer the

viscosity all of these things are are

really important ive highlighted

isotonicity here

but they

they they have to be well thought

through and designed to avoid for

example hemolysis on injection injection

site reactions a pain on injection to

the patient

the volume to administer certainly for a

large volume iv

less constraints but if were talking

about a subcutaneous injection obviously

very volume constrained with regard to

how much we can administer through that

route

um

again talk a little bit about these

types already uh iv parental

formulations typically infusion or

injection

that can be lyophilized powders for

reconstitution at the pharmacy

or a readymade solution for an

injection these are typically delivered

in the infusion center or a hospital

setting

intramuscular injection

interesting

about these they can be very rapid onset

not as quick as iv but still a rapid

onset but can also be effective for

sustained release application

depot injection through formulation

technology

there are again volume limitations site

of administration

limitations um

needle length and

viscosity plays very closely with

syringe ability

and the gauge of the needle making sure

that those are designed to work together

um but its typically a a provider

administered perennial route

subcutaneous injection

very common these days uh seeing more

and more with regard to antibody

therapies the monoclonal antibodies

delivered through subq injections

diabetes

delivered through subcutaneous

injections of diabetes therapies

excuse me and um and they have a

relatively rapid onset of action um

frequently these are selfadministered

dosage forms um

and constraints are are in place with

regard to volume but thats an area of a

lot of innovation these days

with regard to um

the the volume to be able to administer

and as i shared earlier um

patient choice um

the connected devices the insulin pumps

are are all

new subcutaneous

route of delivery um

approaches that i think well see more

and more of

going forward and then lastly

intradermal index injection its a its

fairly specific in in a less common

limited route i wanted to make sure that

we um

uh illustrated that as well you see that

with regard to allergy testing tv tests

and uh and some vaccine in novel

oncology applications uh lastly um i

just wanted to address or or make you

aware of

parental formulation with regard to

subdermal implants and these tend to be

um very longacting implants

to provide a chronic effect for

months or even years

um quickly on nasal drug delivery

this can be

systemic or local

there are certainly

volume constraints with regard to the

amount of material that can be delivered

nasally requires a potent drug

these can be solutions or suspension

nasal sprays they can also be dry

powders um and theres a lot of emerging

data now on uh an investigation on on

using the nasal route to deliver

uh directly to to the brain and and

avoiding in some regards the the

bloodbrain barrier um

these can have a very rapid um exposure

and systemic effect and uh i think its

an area um that will see uh more and

more therapies looking to the nasal

route of delivery going forward

pulmonary inhalations

um advantages here are really a very

higher local concentration um to the

target tissue the lung um it avoids the

first pass effect of the oral route and

the

higher exposure of

drugs to other potential organs

by going directly to the lung these are

frequently selfadministered

preparations

um some disadvantages are as you might

expect

you know potential toxicity to the lung

tissue itself either through the drug or

from the formulation components um

it and has the potential over a long

chronic use period to alter the natural

lung defenses and so this is something

that

a lot of science and engineering going

into ensuring that the way that these

products are are designed and formulated

can really minimize that risk you can

get systemic exposure

through the lungs and so another very

important consideration

with regard to

potential offtarget toxicities

for these types of products and it

really requires a very thoughtful

careful particle design

strategy and device design strategy as

well

transdermal patches are something that

can be very effective for certain

patient populations um it can be uh

really serve as a

kind of a modified release or a longer

acting dosage form um the dose to

deliver is really typically very limited

um but the end and the drug itself needs

to be able to be absorbed through um the

skin a lot of times well see the use of

um permeation enhancers um sometimes

those permeation enhancers can in

themselves cause irritation or or have a

deleterious effect

typically we need to rotate the site of

application um but the dosage form is

discrete um and it and it can be an

effective way to deliver therapy in this

instance um uh you know for alzheimers

patients um to help cognition

with the exelon rippostigmine patch

um topical ocular odoric formulations

are all

ways that drugs can be delivered

they all have their specific

utility

were really targeted for local action

in most instances

i draw your attention to we talked about

modified release

earlier in the use of polymers

to the occu cert pilocarpine

product that ive illustrated here

employs a lot of the same

membrane and drug releasing uh

technology that we talked about for the

modified release um in the oral use

scenario but important to note that

these are also sterile preparations for

the eye for the year and um and so all

the considerations around sterility

play a very important role with these

types of formulations as well

vaginal and rectal suppositories not a

very common

dosage form but certainly one that can

be used for both local or systemic

delivery can accommodate higher doses um

and

and typically we see this either special

patient populations or

in the in in the event that nausea or

emesis would prevent an oral ingestion

and and vaginal

suppositories are typically for

um for local therapy

so coming to the end here um talk a

little bit about packaging and labeling

and i referred to this earlier um its

really that holistic

design of the product so the formulation

we spent a lot of time talking about

um but the way that formulation is is

presented is critically important as

well how will it be packaged will it

maintain this the packaging maintains

stability will it be able to be shipped

and stored um and maintain its its

activity um

how will the dos form be administered

will a device be required if so who will

use that device and how is that designed

um and the instructions to the caregiver

for how to use that device can they

really be understood um i share this

image of an oral dosing syringe to

highlight um a point that of emphasis in

the united states around the way that

devices are are created and in this

instance you can see a scenario where

theres actually two scales on this

syringe which is really not a good

practice

in this instance there can easily be

confusion with regard to

the user with which scale should i use

and if the instructions said to deliver

two mills it would not be

the scale on the right hand side it

would not be uncommon um in human factor

studies to see a use error for the where

the user would actually draw it up to

the two on the left side of the scale

which is a two teaspoon

amount to administer and effectively a

x overdose of the drug and when

particularly for oral liquids that

patient population tends to be children

this could be a very serious adverse

outcome

quick word on alternative administration

um we spent a lot of time talking about

the design of the device a design of the

dosage form and how they could or should

be used unfortunately our products cant

always be used

as are taken as designed and so as a

formulation scientist we also think a

lot about con

potential alternative use scenarios how

could our product be modified for

example to administer through a g tube

or an ng tube

would you disperse a capsule or a tablet

would that plug the tube what about

compatibility

what about using food um to administer i

i i have an excerpt here from

uh uh product labeling for the or camby

pediatric uh oral granule dosage form

that illustrates a very specific

information to be provided on the

appropriate way to use and administer

the dosage form but the key message here

is

while

there are many many ways in the real

world that patients may use our products

its really important not to be so

focused on communicating all the things

that they can do but more importantly if

there is something that we know that

they should not do if there is a risk

associated with the drug its

manipulation its stability we need to

make sure that were communicating that

in the product label

we talked a little bit about these

special patient populations and they

deserve special consideration in

formulation development a lot of

legislation over the last years or so

in both the us and europe around

pediatrics im anticipating legislation

around

elderly designing for elderly patients

and certainly always that specific

disease state um

consequence to the patient where maybe

theyre suffering for dysphagia and

parkinsons disease or or psp and and

these are things that we need to really

be paying attention to

so in summary its about bringing all of

these um domains together the patient

considerations the technical

considerations at times business

considerations and ensuring that were

developing high quality safe and

efficacious formulations

and um and so i hope that after this uh

lecture you have uh better understanding

of some of the key um learning

objectives that we stated at the

beginning and with that id like to

thank you very much for your attention

and have a great day