the next lecture will be by dr robert

dr shuck is a clinical pharmacologist in

the genomic and targeted therapy group

at the fda

in his current position dr shuck

contributes to the regulatory review of

investigational new drug applications

to effectively utilize genomic and

biomarkerbased strategies in drug

development and regulatory evaluation

prior to joining the fda robert received

his doctorate of pharmacy degree from

the university of michigan college of

pharmacy and then completed a phd in

pharmaceutical science at the university

of north carolina school of pharmacy

please enjoy todays lecture

hi my name is robert shook im a

clinical pharmacologist in the center

for drug evaluation and research at the

fda and today well be speaking about

biomarkers of drug effects

going to break the lecture up into three

separate parts im first going to

discuss biomarker definitions and

utility ill then go on to discuss the

use of biomarkers in drug development

including pharmacodynamic biomarkers as

well as surrogate biomarkers and then

were going to discuss briefly some

regulatory considerations in the use of

biomarkers

so the first section will be on will be

the definitions and utility of

biomarkers

so what is a biomarker a biomarker which

is short for biological marker generally

refers to a measurable indicator of some

biological state or condition

biomarkers are often measured and

evaluated to examine normal biological

processes pathogenic processes or

pharmacopharmacological responses to a

therapeutic intervention and biomarkers

are used in many scientific fields as

well as medical practice so theyre used

both in in science and drug development

as well as in clinical practice in the

care of patients

biomarkers are not new however the

application of novel biomarkers in drug

development and regulatory decision
making is a current area of focus for
many healthcare stakeholders including
pharmaceutical industry academia health
authorities and patient advocacy groups
so in addition over the last decade or
so there have been numerous adv
technological advances in our ability to
measure and quantify biomarkers so this
has led to the discovery of many new
biomarkers and many new techniques such
as next generation sequencing have led
to this being a very active area of
research currently and were trying to
figure out how best to utilize
biomarkers both in patient care as well
as in drug development to improve
efficiency and improve care
so why are biomarkers important in the
clinical setting biomarkers allow us to
diagnose disease which is the foundation
of therapy they allow us to monitor the
disease process you can determine if a
patient is getting better or getting
worse and adjust their therapy
accordingly

theyre used to monitor response and

toxicity to therapies so you can

determine if a patient has too high or

too low of a dose potentially and then

go on to adjust that dose to have an

appropriate therapeutic window for that

patient

in the therapeutic product development

setting biomarkers can inform the safety

and pharmacologic activity in early

nonclinical studies of a drug or of a

candidate drug

they can be used for proof of concept in

early clinical studies to demonstrate

that your drug is

getting to the target site and having

some sort of action

they can be used to determine doses for

later confirmatory confirmatory efficacy

trials

they can be used to actually demonstrate

efficacy in later phase studies if its

a surrogate biomarker which ill discuss

in more detail in the next section

and also they can be used to demonstrate

toxicity in all stages of drug

development

so despite the widespread use of

biomarkers until recently there was not

a wellaccepted standardized definition

in for biomarkers or categories of

biomarkers for their use so a couple of

years ago the nih and fda collaborated

to create a biomarker working group and

they created what they call the best

resource and this stands for biomarkers

endpoints and others other tools

resource and what this is is a glossary

of terminology and uses of biomarkers

and endpoints in basic biomedical

research medical product development and

clinical care this is a freely publicly

available resource its available at the

link thats on the slide thats

currently being shown so you can go and

access that and its actually meant to

be a living document so its going to be

updated from time to time as the field

evolves

so best defines biomarker as a defined

characteristic that is measured as an

indicator of normal biological processes

pathogenic processes or response to an

exposure or intervention including

therapeutic interventions and they

recognize five different types of

biomarkers including molecular so this

could be a genotype of a patient

histologic so this could be information

from a

slide from a tumor

biopsy

radiographic biomarkers such as imaging

biomarkers again very useful in oncology

as well as other settings and

physiologic characteristics so this

could be something such as blood

pressure

this slide has several examples of

biomarkers these are what are considered

traditional or standard biomarkers

youve probably all heard of all of

these

things such as blood glucose and

cholesterol are measured in medical

practice as well as used in the drug

development setting

things such as transaminases bilirubin

and alk foss are used to assess liver

function serum creatinines creatinine

clearance and cystatin c can all be used

to assess kidney function and again

these are traditional biomarkers that

have been found acceptable over time

through clinical experience and weight

of evidence so theyre well accepted in

many different settings people arent

really going to question their use

theyve got many different uses however

not all biomarkers going to are going to

have this level of data and this history

of of use in medical in medical the

medical setting

so theres a need to develop standards

to

to standardize these biomarkers so that

they can be used within certain contexts

in drug development and ill discuss

that in the third section today

so the last slide showed many different

types of standard biomarkers but i want

to point out that a biomarker can take

on many different forms so this is a

slide with different biomarkers for

cardiovascular disease and organizes them into several different categories based on what theyre used for so they recognize functional biomarkers and these can be things such as exercise testing or assessments of endothelial function or vascular function they recognize quality of life biomarkers so this could be the results of a patient reported outcome questionnaire could be considered a biomarker

a medical device derived biomarkers so things so information thats gained from things such as implanted icds or sensor patches can be considered a biomarker

imaging biomarkers again echocardiography or mri can be biomarkers and lastly molecular biomarkers and this again is the the category thats probably gotten the most attention recently due to advances in technologies these are things such as proteins peptides mrnas or genetics they can be measured in blood or urine samples

and these can also be very useful

biomarkers

similarly this slide shows different

potential biomarkers for prostate cancer

and this is

organized by the where the biomarkers

are originate so the imaging biomarkers

such as trans rectal ultrasound or ct or

mri or pet imaging

serum biomarker so you can look at

circulating tumor cells in the serum as

well as molecular analyses and dna and

rna

the tissue biopsy biomarkers so

histopathology information gleason score

immunohistochemistry or you can do

molecular analyses actually on the tumor

tissue to look for somatic mutations and

changes in gene expression and lastly

urine biomarkers so theres many

different metabolites that are useful to

measuring urine for prostate cancer

patients so biomarkers can take on a

very broad array of things not just the

traditional biomarkers that youve

likely heard of such as blood pressure

and glucose

so best recognizes eight different

categories or categories of biomarkers

and they can be used for many different

things so susceptibility biomarkers can

inform whether or not youll develop a

disease

an example of this would be braca

mutations for breast cancer they can

inform the the lifetime risk of a

patient for developing breast cancer

a diagnosis of disease so do i have an

actual disease so glomerular filtration

rate in chronic kidney is diagnostic of

chronic kidney disease

prognosis so how will i live longer psa

changes can be informative a prognosis

for prostate cancer

prediction well i respond to treatment

so certain braf mutations for some

melanoma treatments can inform your

likelihood of response to that drug so

if you have that predictive mutation you

might that might be a good drug for you

whereas if you dont have that

predictive mutation then the drug youre

unlikely to respond to that drug and

therefore a different line of therapy

would be more appropriate so thats a

predictive biomarker

response so did the treatment work so an

example of this would be inr as a as for

a response of warfarin in the treatment

of stroke or in the reduction of risk of

stroke so inr within a certain window is

informative of a likelihood and a

decrease of your risk for stroke

so this can inform whether or not the

treatment is working appropriately

monitoring has the condition changed hiv

rna levels are commonly measured in hiv

and aids patients to monitor disease

process

and safety biomarkers so am i having an

adverse event so alt levels can be

informative of whether hepatotoxicity is

occurring at a very early stage and

therefore you can monitor this as a

safety biomarker and potentially stop

the drug or alter the dose to prevent

worse hepatotoxicity from occurring

and lastly id like to just note that

these functions are not mutually

exclusive so theres theres much

overlap in these so for example i used

inr as a response biomarker for warfarin

in the reduction of the risk of stroke

however this is also considered a

monitoring biomarker because patients

that are taking warfarin they monitor

their inr regularly to make sure theyre

in the appropriate therapeutic window

and it could also even be considered a

safety biomarker because if inr goes

above a certain level it increases your

risk for bleeds and therefore it could

be considered a safety biomarker for

that drug as well so these are not

mutually exclusive

now that ive discussed the many

different categories of biomarkers i

want to focus in a little bit more

narrowly on the ones that are considered

that could be considered efficacy

biomarkers or biomarkers of drug effect

so the first i want to talk about is a

pd or response biomarker so this is a

biomarker used to show that a biological

response has occurred in an individual

who has been exposed to a medical

product or environmental agent

an example of this would be sweat

chloride can be used as a

pharmacodynamic or response biomarker

when evaluating patients with cystic

fibrosis and its used to assess the

response to cystic fibrosis transm

transmembrane regulating regulator

potentiating agents

also hemoglobin ac may be used as a

pharmacodynamic or response biomarker

when evaluating patients with diabetes

to assess response to antihyperglycemic

agents or lifestyle changes and i chose

these two examples specifically because

the sweat chloride could be considered

more of a true pd biomarker we havent

actually approved any drugs based on

this endpoint in clinical trials yet but

it is very informative of whether a cftr

potentiating agent is having some

activity in a patient

on the other hand hemoglobin ac is a

little bit more established this

biomarker has been actually used to

approve some drugs with some antihyperglycemic agent so it could actually be considered a surrogate biomarker

safety biomarkers so just to point out safety biomarkers can also become a biomarker of an effect its just a biomarker of a negative effect so best defines a safety biomarker as a biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood presence or extent of toxicity as an adverse effect a couple of examples of these would be hepatic amino transferases and bilirubin may be used as safety biomarkers when evaluating potential hepatotoxicity

a neutrophil count may be used as a safety biomarker when evaluating patients on cytotoxic chemotherapy and they can be used to adjust dose determine the need to interrupt therapy or consider the use of growth factors so they can be an early safety signal that you can can use to monitor a patient and

adjust the medication accordingly to

prevent a worse toxicity from occurring

surrogate endpoints so best defined

surrogate endpoint as an endpoint that

is used in clinical trials as a

substitute for a measure of how a

patient feels functions or survives

and it actually recognizes three

different categories of surrogates based

on the quantity and quality of evidence

that that supports their use as a

surrogate

so the first is a validated surrogate

endpoint

this is an endpoint thats supported by

a clear mechanistic rationale and

clinical data providing strong evidence

that an effect on the surrogate endpoint

predicts a clinical benefit therefore

this can be used to support traditional

drug approval without the need for

additional efficacy information so this

can be a standalone endpoint in an

efficacy trial for a drug

the next category is reasonably likely

at surrogate endpoint this is an

endpoint supported by clear mechanistic

and or epidemiologic rationale but

insufficient clinical data to show that

that it is a validated circuit endpoint

so in this case we have a little bit

less data indicating that its a valid

surrogate and therefore these endpoints

can be used for accelerated approval of

drugs for expedited access for medical

devices and ill cover the difference

between traditional and accelerated

approval a little bit more in depth in

the next section but a reasonably likely

surrogate can be used for accelerated

approval purposes

the last category is a candidate

surrogate endpoint and this is an

endpoint thats still under evaluation

for his ability to predict a clinical

benefit so this could be anything that

has some data showing that its a

potential surrogate but not enough data

to truly be able to know how it can

effectively be used or appropriately be

used

next id like to cover some examples so

an example of a validated surrogate endpoint would be blood pressure reduction is a validated surrogate endpoint for reduction in rates of stroke myocardial infarction and mortality and has been used for the basis of approval for drugs intended to treat hypertension

so this slide shows the example of some data that can be used to demonstrate that a surrogate is a validated surrogate and it has each of these dots on the slide actually is a clinical trial endpoint not an individual patient and they shield it across all these different clinical trials which many of these are many tens of thousands of patients overall i believe that representation is over a half a million patients included in these clinical trials and they show that theres a relationship between on the xaxis the the blood pressure reduction that was observed in these trials and on the yaxis the wa the odds ratio of a cardiovascular event so you can see

across multiple different trials that

had multiple different drugs from

multiple different drug classes we see

that this blood pressure lowering effect

reduces our risk of cardiovascular

events and this is great data to show

that this is a validated surrogate

endpoint for

for antihypertensive agents

now an example of a reasonably likely

surrogate endpoint theres a couple of

these on this slide including

radiographic evidence of tumor shrinkage

so this would be response rate as well

as progressionfree survival and certain

cancer types have been considered

reasonably likely to predict an

improvement in overall survival with

certain therapies and therefore theyve

been used to support accelerated

approval of drugs to treat these cancer

types so in some cancers but not all

cancers we consider radiographic

evidence of tumor shrinkage to be a

reasonably likely surrogate

second example is outcomes of sixmonth

followup treatment so sputum cultures
and infection relapse rate have been
considered reasonably likely to predict
the resolution of pulmonary tuberculosis
and have been against used to support
accelerated approval of drugs to treat
tuberculosis
and theres no node graph showing all
the different data on these and these
ones because again if there was that
sort of data supporting it it would be
considered a validated surrogate theres
not quite as much data so its
considered a reasonably likely surrogate
for these two examples and i wont cover
candidate surrogate biomarkers because
again these could be you know anything
with some data indicating that its a
potential surrogate but not enough that
we know how we can can effectively
utilize them
so now that ive covered the definitions
and utility of biomarkers id like to to
go over using biomarkers in drug
development and how they can be
effectively utilized in clinical trials

this slide shows the outcomes of a study

that was conducted a few years ago at

astrazeneca and what they did was they

looked through they looked over their

product portfolio for the previous few

years and they tried to determine what

the key contributors to drug development

success were and the things that they

identified as identifying successful

projects as opposed to projects that did

not make it to market or projects that

were considered failures were having

the right target the right tissue the

right safety profile

the right patients identified for the

for the drug and the right commercial

potential and what i want to point out

here is that in order to determine these

things youve got to be able to have

some kind of data to support whether or

not you have the right target the right

tissue the right safety profile etc

and all biomarkers can be utilized to

inform virtually all of these things and

ive underlined on the slide the

examples where they specifically mention

having biomarkers to determine these

things but its not really limited to

those theres many of the other things

that are listed on this slide can be can

be informed by appropriate use of

biomarkers so this is why biomarkers are

considered so important in drug

development setting

im not sure what experience everybody

has with clinical studies but to to

discuss the use of biomarkers throughout

drug development we need to kind of make

sure that were on the same page as far

as the different phases of clinical

studies so i briefly want to cover that

in this slide

so phase one clinical studies are the

initial introduction of an

investigational new drug into humans

these are frequently in healthy subjects

and the goal of these is

to obtain some pharmacokinetic

pharmacodynamic and safety information

to design scientifically valid phase two

studies now your phase two studies are

your early controlled studies to get

information on the drugs effectiveness

in the target patient population so here

were moving into patients studies are

slightly larger usually and theyre in

the actual target patient population to

determine if the drug is having the

appropriate effect

and lastly phase three studies are your

adequate and wellcontrolled studies to

gather information about effectiveness

and safety that is needed to evaluate

the overall benefit risk

relationship for the drug for marketing

so overall your goal here is to

demonstrate substantial evidence of

effectiveness and a positive benefit

risk profile in order to get the drug on

the market

so how are drugs approved under the food

drug and cosmetic act states that the

fda cannot approve an application to

market a drug unless there is

substantial evidence that the drug will

have the effect it purports to have

and this evidence of efficacy is

primarily derived from adequate and

wellcontrolled clinical trials that
demonstrate improvement based on a
clinical endpoint that directly measures
how how a person feels functions or
survives so those are
thats a very important concept these
fields functions are survived endpoints
are considered clinical endpoints
theyre often referred to as hard
outcomes in clinical studies so if you
improve how a patient feels such as
reduction in pain how they function such
as improvement and activities of daily
living or sixminute walk tests or
something of that sort thats a measure
of function or how they how long they
survive those are considered clinical
advocacy endpoints and are generally the
basis for drug approval
however there are exceptions built into
this where
wellestablished surrogate endpoints can
be used to approve a drug however this
term is not defined but this would kind
of be the the category of the validated
surrogate endpoints under best and

reasonably likely surrogate endpoints
under the accelerated approval program
so the accelerated approval program is
meant to address diseases that are
serious medical conditions where theres
an unmet medical medical need so a
patient population that doesnt have any
drugs available with a serious disease
they allow reasonably likely surrogates
to to be the basis of approval under the
accelerated approval program to get
those patients a drug the drug
however this does require a confirmation
study so in the postmarket setting they
have to do a confirmation study on a
field functions that survives clinical
endpoint in order to maintain marketing
for that drug
so how can biomarkers be used to inform
drug development they can be used in
virtually every different stage so even
back in the preclinical studies in your
basic clinical re or your basic research
when youre trying to identify pathways
and identify potential drugs they can
inform drug target selection so what

what pathway you want to target for a

certain disease they can inform the

drugs mechanism of action

once you get into clinical studies they

can be used in in phase one through

three as well as even in in

postapproval studies to stratify

patients so if theres a predictive or

prognostic biomarker that you think

might affect your outcomes and you want

to make sure that you have equal numbers

of patients in in each group in your in

your drug group and in the placebo or in

the comparator group you can stratify

patients and this can can eliminate some

noise from your clinical studies they

can be used for safety assessments for

patient selection and enrichment to help

determine the appropriate dose selection

as well as again in efficacy assessments

so how are efficacy biomarkers used in

drug development basically theyre used

to measure response to a treatment and

this can take on several different forms

in your earlier phase studies they can

be used to establish a biological effect

this would be a use of a pharmacodynamic

biomarker in early trials and this

basically shows target engagement your

drug is getting to the target and its

having some sort of effect that you

consider desirable

they also can be used to determine

suitable doses and regimens to carry

forward into later phase studies

and lastly they can be used to replace

health outcome endpoints and this again

would be the surrogate endpoints in in

later phase trials

the idea here the the promise of of

using surrogate biomarkers is that they

promise to shorten clinical trials and

reduce trial size and the way that they

do this is that generally your your

surrogate biomarker the change in that

is going to occur at a time point before

the actual clinical endpoint is going to

occur so you can have a shorter trial

they can also be re used to reduce trial

size because generally a surrogate

biomarker is going to have less noise

associated with it than a true clinical

endpoint so it as a survival endpoint is
very hard to demonstrate because not
only is your drug having an effect on
that but patients lifestyle and things
of that sort are also impacting
the the clinical efficacy endpoint so
therefore a surrogate biomarker can be
used to reduce the trial size because
theres going to be less noise
surrounding that end point so shorter
clinical trials and smaller clinical
trials can be much more efficient
because the larger and the longer
clinical trials get the more expensive
they are and the harder they are to
conduct
and also again the basis for accelerated
approval under the
accelerator approval program and also
can often support full approval in the
case of validated surrogate endpoints
heres an example of the use of
biomarkers to determine dose so this is
the drug belimab which is a b lymphocyte
stimulator inhibitor so it exerts its
effect through lowering b cell counts

and they in this case they looked over

multiple different b cell subsets and

they looked over a couple of different

doses

and they used this data to determine

that the higher dose was having a

greater effect on the b cell subsets and

they use this information to help inform

their dose and ultimately the approval

of the drug

so how are safety biomarkers used in

drug development safety biomarkers are

used to identify and monitor potential

drugrelated toxicities so in early

phase animal studies you can conduct

toxicogenomic studies to evaluate safety

they can also be used to help determine

the starting dose for first in human

trials so this is calculated from the no

observed adverse effect level or noel in

toxicology studies and biomarkers can be

can be used to inform this and then you

base your first and human starting dose

on that

they can be used to identify monitor and

avoid toxicities in clinical trials

and they can again also be used to
determine the appropriate dose so you
want to have a dose below you when you
start seeing toxicity and in some cases
they can actually be used to inform dose
reduction schemes so this is very common
particularly in oncology and diseases
where we dose at the very high end of
the dose response curve where because
the disease is very severe were trying
to squeeze every bit of efficacy out of
that drug and were willing to tolerate
some some safety or adverse events and
therefore you can use biomarkers to
monitor safety biomarkers to monitor
potential toxicities and before you have
a clinical issue occur you can adjust
the dose or have a dose interruption for
that drug
so here we have a very simplistic view
of drug effects
and when were trying to determine which
biomarker we want to look at in drug
development the simplistic view would
have the drug interacting with the
target

this then leads to some change in a

biomarker which then is predictive of

your clinical outcome so how the patient

feels functions or survives

however biology is rarely that simple so

this is a more realistic view of how of

how biomarkers change in response to a

drug so here you have the drug

interacting with a target

this myriad of changes occur in

different biological pathways some are

in the causative pathway some might be

parallel some are in

sequence with each other and then you

know the changes in these these

biological pathways ultimately produce

some change in clinical outcome and

again how a patient feels functions or

survives so any of these green or red

dots here could be a potential biomarker

that we would measure in drug

development to determine if our drug is

having an effect

and therefore we need to decide which

one or ones we want to look at and this

can the basis of this can be based on

what we actually want to show depending

on where were at in drug development

and ill cover that over the next couple

of slides

so heres an example of efficacy

biomarker for an ace inhibitor so here i

have the

reninangiotensin aldosterone pathway

and this is also again a simplified look

at that but most of the important

components are here so in the renal

angiotensin aldosterone pathway we have

angiotensinogen is converted by renin

into angiotensin one the angiotensin

converting enzyme then converts

angiotensin one into angiotensin ii

which acts via the angiotensin ii

receptor to cause aldosterone secretion

sodium and fluid retention sympathetic

nervous system activation and

vasoconstriction this leads to an

increase in blood pressure and this

causes hypertension so hypertension

although recognized as a disease is also

in itself kind of a biomarker or a

surrogate of increased risk for stroke

and cardiovascular events

so ace inhibitors are drugs that inhibit

this angiotensin converting enzyme from

converting angiotensin one into

angiotensin ii

so anything downstream of here could be

a potential biomarker to show efficacy

or drug effect with an ace inhibitor

so one potential biomarker assuming that

there was an analytically validated way

to measure it would be angiotensin ii

so the advantage is that angiotensin

is very proximal to the drug target

however its very distal from the

clinical outcome

so this would make it a candidate

biomarker to demonstrate drug activity

however it makes it a poor candidate as

a surrogate biomarker and the reason for

this is because its very proximal to

where our drug is having its action its

actually the the product of the enzyme

that were inhibiting

it can be very sensitive to inhibition

of that enzyme

however because its so far from our

outcome of hypertension a lot of

different things have to happen before

the drug actually exerts that clinical

effect and a lot of compensatory things

can kick in and other things can happen

that actually prevent the drug from

ultimately having the effect on

hypertension so it would be a poor

surrogate outcome because so much has to

happen before that that out that

clinical efficacy actually occurs but

its a very sensitive mile marker to

demonstrate drug activity so we could

use this in our early studies as a

pharmacodynamic biomarker to show that

our drug is getting to the target site

of action potentially informed doses for

our later face studies

now alternatively we could look at blood

pressure as a biomarker of effect for an

ace inhibitor now blood pressure in

contrast to angiotensin ii is very

distal from the drug target but its

very proximal to the clinical outcome

this makes it a good candidate surrogate

biomarker however its problematic

biomarker for demonstrating drug

activity and the reason for this is

again because so much has to happen

between the the inhibition of the enzyme

and and the the change in blood pressure

that a lot of compensatory things can

kick in and its very its going to take

a larger study with more patients to

show an effect on this biomarker so when

youre in an early phase study you might

not want to invest that much into a very

large study with a lot of patients to

demonstrate that it that it has a change

in blood pressure

so you might instead monitor angiotensin

ii again as a pharmacodynamic biomarker

whereas when you get to your later face

studies and youre trying to truly show

an effect this would be a candidate

surrogate biomarker to look at in your

later phase efficacy studies

so returning to our simplistic view of

drug effects after the drug interacts

with this target we have a choice of

many different biomarkers that might

change in response to that that are

ultimately we hope predict clinical

outcome but where that biomarker is and

what properties it have it has can

affect how we want to use utilize it for

drug development

now that ive covered the the different

types of biomarkers and pharmacodynamic

biomarkers versus candidate surrogate

biomarkers i want to discuss

the issues associated with using

surrogate biomarkers in in drug

development programs so again surrogate

endpoints are defined as an endpoint

that is used in clinical trials as a

substitute for a direct measure of how a

patient feels functions or survives

different factors that should be

considered when youre deciding whether

or not to use a surrogate endpoint would

be biological plausibility

its success in previous clinical trials

and predicting outcomes

and the risk benefit and public health

considerations of the drug so this is an

actual related the biomarker but its

more of a public health consideration

and a standard of care uh how how the

medical practice is currently

occurring in this patient in the patient

population that youre interested in

so for biological possibility things

that favor the use of surrogate include

epidemiological evidence thats

extensive and consistent across studies

a quantitative relationship

a credible animal model to show drug

response and a wellunderstood disease

pathogenesis and drug mechanism of

action and also again the surrogate

being relatively late on the biological

path

things that do not favor surrogates in

terms of biological plausibility are

basically all the opposites of that so

inconsistent epidemiology

no quantitative epidemiological

relationship no animal model unclear

pathogenesis and unclear drug mechanism

and the research the surrogate being

remote from the clinical outcome

as far as clinical trials success so

effect on a surrogate has predicted

outcome with other drugs of the same pharmacological class this can be supportive of it being a surrogate for another drug in that same class whereas if theres an effect on surrogate has predicted outcome in several different classes this supports more general use so this would be the difference between say for an antihypertensive drug if you had a diuretic and it had only been shown to predict outcomes with other diuretics versus if itd been shown to predict outcomes with other classes such as ace inhibitors and calcium channel blockers and other antihypertensive agents that would support more general use for another antihypertensive agent from another class

things that dont favor the use of surrogates in clinical trials would again be the opposite so negative outcomes in clinical trials without a clear explanation for that as well as inconsistent results across

drug classes

so the last factor here that is

discussed is the risk benefit and public

health considerations so in cases where

you have a disease thats serious or

lifethreatening with no alternative

therapies youre going to be more likely

to accept a surrogate for that that type

of a disease because the the stakes are

we really want to get patients those

drugs and therefore were willing to

accept a little bit of uncertainty for

the efficacy

because we we those patients have no

other alternatives available to them

a large safety database again if the

drug has been shown to be very safe and

were confident in that

its more likely to use a surrogate

shortterm use of the drug as well as if

theres difficulty in studying the

clinical endpoint

things that do not favor the use of a

surrogate in terms of public health

considerations or a nonserious disease

and if theres alternative alternatives

available for patients with that disease

a little safety data so if were not

confident in the safety profile we want

to see improvements in those hard

outcomes or clinical efficacy endpoints

longterm use of the drug

and if the and the clinical endpoint is

easy to study theres no reason to use a

surrogate instead you can just study the

clinical outcome

and lastly if theres a long delayed

small effect in relatively healthy

patients this would not support the use

of a surrogate

so the next few slides here are adopted

from a paper by dr thomas fleming who

has spoken extensively on the the

subject of surrogates if youre

interested in surrogates at all i highly

recommend that you read the the

reference there and he has a couple of

other papers which are fairly easy to

identify or defined as well

he has many different informative papers

on this on this subject but ill attempt

to go through some of the main

considerations that he lists and the

cautions for use of surrogates and the

reason that we often have to be cautious

is because theres a lot of candidate

surrogate biomarkers that are

biologically plausible and they seem

like theyre theyre sure to predict the

clinical outcome however theres reasons

that they often fail to be uh end up

being validated surrogates and and

several of these are discussed over the

next couple of slides

um the first one so in the first case

here at the top of the slide were

discussing the

the transmission of hiv from mother to

child so in this case we have hiv viral

load is causative of that transmission

of hiv from mother to child however many

things are going to also be correlated

with hiv viral loads such as cd so if

you have a biomarker such as cd its

also going to look like its associated

with the the transmission however we

have a drug that affects our cd levels

without impacting hiv viral load its

not going to affect that transmission

the example at the bottom of the slide

is fairly similar so tumor burden is

causative of cancer symptoms and death

and but there are many biomarkers that

are going to be associated with with

tumor burden such as cea or psa so if we

were to have a drug that were to affect

those those biomarkers ca or psa without

actually impacting the tumor burden of

the patient its not going to go on to

to

change the cancer symptoms or likelihood

of death in those patients so if its

correlated with the the true with a true

biomarker or if its correlated with the

clinical outcome but its not in a

causative pathway that could it could

lead to it not being a good surrogate

the second slide for caution of

surrogates here discusses a couple of

different issues

so the the example on top in this detail

this example is discussed in detail on

the paper

however it discusses patients the

patient population is post myocardial infarction and the use of thrombolytic agents so in this example they discuss they have a novel thrombolytic agent in a smaller phase two study it had a better impact on the what they were considering as a surrogate outcome of timmy blood flow which is a measure of blood flow to the myocardium which is considered a surrogate for 0day mortality so their novel drug had had a better effect at i believe it was the 0 and 90minute endpoint or time points on timi blood flow so they their hypothesis based on that was that this would lead to a better 0day mortality outcome with their novel drug however when they ran their larger phase study they showed that it was actually numerically worse than the older agent and that it did not in fact go on to improve 0day mortality so they investigated the reason for this and possible causes and one thing that they discovered was that in that initial phase two study

the the novel agent didnt actually had
inferior improvement in timi blood flow
at the 0 minute time point so perhaps
having that earlier restoration of blood
flow was actually more important than
the the greater magnitude at the later
time points and therefore this was
unable to predict 0day mortality so
even though it seemed like a
great potential surrogate outcome not
measuring it at potentially the correct
time point led to this not being a
validated surrogate for this disease
and because they monitored the clinical
outcome they were able to determine this
uh the example on the bottom kind of
gets at the the opposite situation and
that is youre youre by using a
surrogate you can sometimes potentially
lead to the conclusion that your drug
does not have an effect when in fact it
does so they start they discuss a study
for in chronic granulomatous disease
and they were using an interferon gamma
as an agent and they considered using
bacterial killing to prevent recurrent

as a surrogate for recurrent serious

infections

they ended up actually looking at the

clinical outcome instead and that was a

good thing because interferon gamma did

not have an effect on bacterial killing

but actually did have an important

effect on recurrent serious infections

so the case here is that you have

actually multiple causal

pathways that are leading to the

clinical outcome of recurrent serious

infections and interferon gamma affected

one of these that was not captured by

the surrogate or the potential surrogate

of bacterial killing so again it can

also lead to a false conclusion that

your drug does not have a positive

effect when in fact it does

and the last slide the the last figure

in this paper that i want to cover is

this discusses the situation where you

have an intervention that has an effect

on a biomarker which you believe

predicts a true clinical endpoint

however the drug might also have art

offtarget effects that could then

cancel out the benefit that youre

observing uh based on the biomarker so

an example of this would be to stick

with hypertension since ive discussed

that in a few different ways a diuretic

might have a positive impact on the

biomarker of blood pressure which

predicts the true clinical endpoint

however if it caused a lot of

hypokalemia which is a known side effect

of many diuretics this could potentially

cause negative effects which would then

cancel out the true clinical endpoint

benefit

so ive discussed in detail a lot of

aspects of surrogate endpoints as well

as pharmacodynamic endpoints so to

quickly summarize these and summarize

the takehome message

surrogate endpoints are important in

drug development because they can

increase clinical trial efficiency it

does this via shorter duration of trials

because the surrogate general the change

in the surrogate will generally occur at

an earlier time point than the change in

the clinical efficacy outcome and it can

do this using fewer patients so you can

power your trial with less patients to

show the benefit that you want to show

this this really leads to much more

efficient drug development

factors that favor surrogate use include

biological plausibility success in

predicting outcomes for multiple drugs

and drug classes and unmet medical needs

for the patient population

however caution is generally advised

when using surrogates because a lot of

candidate surrogate endpoints do not end

up being great predictors of the

clinical efficacy outcome

and again many many surrogate biomarkers

are ultimately shown to be poor

surrogates

so before i move on to the next section

i want to briefly just discuss the

considerations for measuring biomarkers

so measuring biomarkers is often

overlooked but this is extremely

important so whether were in the

clinical care setting where were making

judgments on how were going to treat a

patient or whether were in the drug

development setting where were making

decisions as to whether or not to

continue investigating a drug for a

certain patient population

measuring the biomarker accurately is

extremely important because these are

important decisions and we want to make

sure that were accurately measuring and

that were doing what we think were

doing before we we use that those data

to make those decisions

so appropriate sample collection

processing and storage are all critical

to ensure validity of results

inappropriate can be uh can mean

different things in different situations

so whether youre measuring rna versus

dna you might have to have different

procedures in place for your sample

collection and processing and storage

whether youre measuring something in

blood versus urine for instance can can

have an effect on what appropriate

sample collection and processing and

storage is

analytically validated assays should be

used for quantification of biomarkers

that are used for drug development and

or regulatory decisions and again so

going back to the best definition best

defines analytical validation as

establishing that the performance

characteristic of a test tool or

instrument are acceptable in terms of

sensitivity specificity accuracy

precision and other relevant performance

characteristics using a specified

technical protocol which may include the

specimen collection han collection

handling and storage procedures

uh so just to point out this is

validation that the tests uh tool or

instruments technical performance it is

not validation of its usefulness so

again this is simply the youre

validating the measurement of the

biomarker that youre measuring what you

think youre measuring

it doesnt necessarily mean that just

because youre measuring a biomarker

that its its the appropriate biomarker

to use in a certain situation it just

means that the analytical data are going

to be reliable

so the last thing that i would like to

cover briefly

is the biomarker qualification program

which is currently in the center for

drug evaluation and research and the

website link is on this slide thats

being shown currently

if you are interested in the biomarker

qualification process theres much more

information on the website there

ill briefly uh discover the highlights

or discuss the highlights

so

in many cases standard biomarkers are

not optimal and other biomarkers may

offer better attributes

however every year there are hundreds of

new biomarkers that are reported in the

literature that are potentially have new

useful uh it can are new uses in drug

development or in clinical practice or

might simply be a better indicator of

some process than the current gold

standard but how do we know which ones

are actually valuable for use and how do

these novel biomarkers become the gold

standard instead of the ones that were

currently using

so theres many historically there have

been many different biomarker acceptance

pathways probably the most common one uh

throughout history is simply scientific

community consensus so if theres a

biomarker thats a candidate and theres

many published articles commenting on

that establish its utility

ultimately this will will sometimes lead

to guidances by the fda and regulatory

acceptance in the in the drug

development process or even in the

patient care process

and this but this can often take a very

long time to establish and many

different studies need to be conducted

the drug approval process can lead to

acceptance of a biomarker but this is

generally more narrow so within a

certain drug development program they might use a certain biomarker and thats considered acceptable in that context how and this could make it into drug labels and in the reviews that are conducted by the review staff and sometimes this will ultimately make it into guidance however theres often uncertainty over how exactly this can be appropriately used and more recently theres been the biomarker qualification program so this is a formal process for biomarker qualification its odd theres several different guidances are produced on this theres actual formal fda review of the biomarker for its utility and they are the program often conducts workshops to discuss the need for the standardization of data generation and the data thats needed to qualify a biomarker within a certain context of use so what exactly is qualification

qualification is a conclusion that

within the stated context of use the

biomarker can be relied upon to have a

specific interpretation and application

in drug development and regulatory

review

so what the context of use means is its

a comprehensive statement that fully and

clearly describes the manner and purpose

for of use for the biomarker in drug

development

qualification is a formal regulatory

review and acceptance process of the

biomarker that reaches across all fda

and cedar review divisions so once a

biomarker has been qualified

there you know the different review

divisions wont treat it differently

its qualified for that specific context

of use and can be used across all review

divisions

qualification results in the scientific

acceptance and regulatory certainty and

this is based on a weight of evidence

argument thats presented in the in the

qualification process

what exactly is that process here we

have the biomarker qualification roadmap

the process starts with a letter of

intent this initiates the qualification

process of a biomarker for a proposed

context of use in drug development

next comes a qualification plan this

defines the development of gener uh to

generate the necessary supportive data

to qualify the biomarker for the

proposed context of use

after the the data are generated the

full qualification package is submitted

this contains all accumulated data to

support the qualification of the

biomarker for the proposed context of

use

and lastly theres a qualification

recommendation so this contains the

fdas determination on whether the

biomarker is qualified for the proposed

cou based on a comprehensive review of

the full qualification package so this

is somewhat analogous to drug review

except youre reviewing the utility of

the biomarker within its specific

context of use and it comes to a

determination of whether the the data

are appropriate to support the

qualification of the biomarker for

whatever the context of use

is and the context of use can be very

broad it can be everything from a

toxicity marker for an animal study to

an enrichment biomarker for clinical

studies or it could potentially be a

surrogate endpoint which weve discussed

it could could be qualified for use

so this slide i dont want to discuss in

a ton of detail however its a list of

the biomarkers that have that have

currently been qualified

its fairly short currently but there

are many programs in development as of

right now and the the

rate at which were qualifying them is

actually increasing um so i just want to

point out that it again the diversity

here so theres nonclinical biomarkers

as well as clinical biomarkers and i

believe the first one that was that was

qualified as the the first one on the

page here which is druginduced

nephrotoxicity biomarkers this is in

preclinical studies

more recently things that have been

qualified are prognostic biomarkers for

enrichment of clinical trials

within dominant polycystic kidney

disease

so theres a broad range of things that

can be can be qualified for use and this

can be and this is really driven by

you know what the bottlenecks in drug

development can be so if theres

something where

it currently takes a whole lot of data

to demonstrate that something is safe or

something is effective in a certain

patient population then different groups

can focus in and try to develop

biomarkers that can they can solve those

problems more efficiently and this is

often done this can be done by anybody i

would also like to point out so it can

be an individual company could do this

if they wanted to its often done by

consortia so groups of either academics

or or

industry groups can get together and

pool data to try to make an effort to

qualify a biomarker to help make the

drug development process more efficient

for all of them

so to summarize and

provide some conclusions for the entire

lecture

biomarkers are essential to the practice

of medicine as well as the development

of medical products including drugs

in drug development biomarkers of effect

and safety are used to demonstrate proof

of concept select appropriate doses and

demonstrate efficacy

caution is warranted when using

surrogate endpoints and the biomarker

qualification program can improve

acceptance of biomarkers within a

specific context of use

so with that i would like to say thank

you very much for listening i hope this

has been beneficial to everyone