we are honored to have dr ann zycheck

dr zyck is a boardcertified

pediatrician and a pediatric clinical

pharmacologist who currently serves as

deputy director of the office of

clinical research at the nih

and received a bachelor degree in

pharmacy from duquesne university and a

doctorate of pharmacy degree from state

university of new york at buffalo

she then completed postdoctoral

fellowship training at st jude

childrens research hospital

after that she served as assistant

professor at the university of colorado

school of pharmacy and a clinical

pharmacist at national jewish hospital

in 99

ann entered medical school

at the university of pittsburgh in 99

completed residency in pediatrics at

childrens hospital in pittsburgh

she practiced primary care pediatrics

for two years and then continued her

training in pediatric clinical

pharmacology at stanford university

she subsequently joined the fdas office

of clinical pharmacology and

biopharmaceutics

in 00 she joined the national

institute of child health and human

development

we know you will enjoy dr zychecks

lecture

good afternoon im dr ann zicek im a

pediatrician and clinical pharmacologist

and i want to talk to you today about

pediatric drug development

for disclosure i have no conflicts of

interest to disclose

and the presentation

reflects my views only not those of the

nih or the us federal government

topics i would like to include are the

definition of pediatric drug development

some background legislation

extrapolation outcome measures elements

of a drug development plan

and the need for infrastructure

the definition of pediatric drug

development uh sort of comes in two

flavors the development of an already

marketed drug for a pediatric indication

either which is either the same as the

adult indication using extrapolation of

efficacy with new pediatric dosing and

safety information

or a different pediatric indication

again also requiring new pediatric

dosing and safety information

or development of a new drug for a

pediatric indication

one of the complexities with developing

drugs for children include the

complexity of the fact that youre

dealing with four entire

minimum four

populations the neonates zero to days

and that doesnt even include the

preterm neonates who are

younger up to

as early as weeks gestation an infant

one month to one year of age

child two to ten years adolescent to

years

now we would not be talking about

pediatric drug development if it werent

for some

legislative

information

this is a slide from the 90

congressional record showing the state

of patent medicines in the united states

so

at about this time there were an

enormous number of

easily available compounds with names

like hood sarsaparilla pain celery

compound

uh one in particular that was uh quite

popular was the ms mrs winslow soothing

syrup these were

patent medicines again that had um

proprietary knowledge of the compounds

in them

uh that were freely available and you

can see that they contain chloroform

alcohol

marijuana

huge amounts of alcohol and the one in

particular that created most uh

problem was mrs winslow mrs winslows

soothing syrup

which was advertised for colic and for

teething pain which contained morphine

unfortunately uh there were a good

number of infant deaths from

many of these patent medications

so this was up to about 90 90 there

were these deaths from patent

medications

9

sulfonylamide which was a sulfa

antibiotic

very useful for strep throat

but came in a capsule formulation and so

a pharmacist at massengill decided to

dissolve it in something that would

taste good and he picked antifreeze

diethylene glycol which ended up in

the death of 0

patients

mostly children and the suicide of the

compounder

and in 9 the thalidomide

disaster caused limb deformities again

luckily thalidomide was not approved in

the us

so as a result of basically these

pediatric disasters came regulatory acts

in 90 the pure food and drug act

which required that labels of food and

drugs must truthfully identify the

contents or be pure

9 the federal food drug and cosmetic

act

stated that drugs needed to be safe and

in 9 actually the fda was created and

in 9 the kefalver harris amendment

stating that drugs must be effective for

their labeled indications

now briefly following this there was an

interesting commentary by harry shirkey

who was a pediatrician as well as a

pharmacist

stating that by an odd twist of fate

infants and children are becoming

therapeutic or pharmaceutical orphans in

other words drugs are being developed

for adults

not for children

and so therefore if children were using

these drugs they would be used off label

so in other words being used for

indications that were not in the

labeling or the package insert

so is this a bad idea is off label use

bad

the downside is that every patient is an

n of one experiment there is no data

accrual to learn about safety or

efficacy theres no data accrual to

learn about dosing

and whether the dose should be scaled

from the adult dose

by weight by body surface area and so on

so the goal

from the fda has been to try to attempt

to get pediatric labeling so how do you

do that so the three things that are

required for a drug label are a dose

safety efficacy

should the dose be exposure matched from

adult data

what are the short and long term adverse

events

and in terms of efficacy does the drug

improve

how the patient

feels functions or survives

however again going back to the diverse

patient populations were dealing with

neonates infants children and

adolescents and all the complexity

of those different age groups

so fda has made several attempts to add

pediatric labeling the first one was the

99 pediatric rule

so the feeling was that the

pharmaceutical companies likely had

pediatric data in their files and

the request was would they forward that

data to the fda to improve pediatric

labeling that was not successful

in 99 the feeling was that perhaps a

carrot for the

pharmaceutical industry might help

and the fda modernization act was passed

in 99

99 pediatric rule

00 best pharmaceuticals for children

act otherwise known as bpca and the 00

pediatric research equity act or pria

so the 99 fda modernization act

gave six months of additional marketing

exclusivity that would be granted by the

fda if pediatric clinical trials which

were performed

according to some stipulations of the

fda were completed but not required to

show a positive effect so just the fact

that the studies were done and were

acceptable to the fda review division

was enough to grant that the

manufacturer an additional six months of

marketing exclusivity which could be

fairly lucrative depending on the

product

in 00 the best pharmaceuticals for

children act was passed

this continued the exclusivity provision

of fadama the additional six months

marketing exclusivity

but what was noted in the ensuing time

between 99 and 00 was that many

marketed drugs do not have remaining

marketing exclusivity theyre old drugs

theyre off patent and an additional

provision included a role for the

national institutes of health

specifically the eunice kennedy shriver

national institute of child health and

human development to prioritize

therapeutic areas and medications in

need of improved labeling to sponsor

pediatric clinical trials and to submit

data to fda for consideration of

labeling

this legislation was passed in 00

reauthorized in 00 0 and last month

in 0

and ive been involved with this uh

program since 00

in 00 the pediatric research equity

act or prio was passed this was a

codification of the 99 rule which had

been struck down in court previously

that was a requirement to perform

pediatric studies if it was anticipated

that the drug would be used for the same

indication as adults

now the ringer here was that if the drug

was used for lets say prostate cancer

breast cancer in other words that there

would have to be a prio waiver and the

drug studies would not be performed in

children now this was amended last month

in august of 0

and priya also applies if the molecular

target of the drug is substantially

relevant to pediatric cancer this is

only for cancer but it was it was very

important for the cancer population

so just in terms of whats what here so

we have uh

older drugs with some remaining uh

patent protection or marketing

exclusivity to be covered under priya

newer drugs for the same indication or

the same molecular target for pediatric

cancer would be covered under

and the old drugs which did not have any

patent protection would be uh referred

to the nih bpca program

okay so in planning a pediatric study

the first question you have to ask

yourself is

can the indication of efficacy be

extrapolated from adults to children

then you need some sort of

method to select a dose and monitor

safety so the extrapolation policy at

fda is very useful so if the course of

the disease and the effect of the drug

are sufficiently similar in adults and

pediatric patients then extrapolation

can be applied

does the current adult condition or

indication apply to children in terms of

disease mechanism and the disease course

if the answer is yes then only dosing

and safety need to be shown

for consideration of fda approval if the

answer is no that there cannot be

extrapolation

then the full three studies of efficacy

dosing and safety need to be performed

okay one of the uh main um issues about

doing pediatric drug development is the

problem with pediatric outcome measures

so outcome measures in children in the

short term include

how the patient feels functions or

survives in terms of disease resolution

or improvement in clinical status

longterm effects are also important in

children in terms of growth and

development and this becomes complicated

if studies

require following children for two years

four years into grade school and so on

second question are there pediatric

normal values for outcome measures and i

will show you a few slides where there

are not pediatric normal values

are the outcome measures accepted by the

medical community and the food and drug

administration and i just want to state

here briefly that its important if

youre doing pediatric drug development

that you should be having conversations

with the food and drug administration

the review division responsible for your

drug to determine if youre on the right

path

and does the outcome measure

thats typically accepted makes sense in

a pediatric population

okay i wanted to point out two two terms

just to clarify uh some language well

be talking about

biomarkers a biomarker is defined a

defined characteristic that is measured

as an indicator of normal biologic

processes pathogenic processes or

responses to an exposure or intervention

including therapeutic interventions

and some common examples which we toss

around constantly but dont i think

generally think too clearly about them

are

cholesterol

blood pressure serum creatinine

creatinine clearance so we assume that

when we talk about serum creatinine

creatinine clearance were talking about

kidney function when were talking about

cholesterol

were looking at a cholesterol level as

indicative of your chance of having a

heart attack or a stroke

and this is in comparison to the term

surrogate marker and i thought this was

really well stated by rusty katz

formerly of the fda

the primary difference between a

biomarker and a surrogate marker is that

a biomarker is a candidate surrogate

marker whereas a surrogate marker is a

test used taken as

a measure of the effect of a specific

treatment okay

now these are a couple of tests that

have worked very nicely in adults but
have not functioned well in the neonatal
population the first one is the six
minute walk test this is accepted by the
food and drug administration as an
indicator of functional capacity
its used primarily in adults to measure
cardiopulmonary function
and an adult pulmonary hypertension as a
biomarker of reduction in pulmonary
hypertension and improvement in function
so you have a patient walk as far as he
or she possibly can in six minutes
thats the six minute walk test however
neonates cannot walk and so obviously
this is not applicable to neonatal
pulmonary hypertension so were back to
doing invasive cardiovascular monitoring
another term is blood pressure this is a
surrogate marker for survival of adult
hypertension so if a drug lowers blood
pressure typically can be approved
without
following patients all the way toward
mortality
however we did an interesting study with

the neonatal research network and the

question was uh

surrounded itself with dopamine so

dopamine is used as a presser agent to

increase blood pressure in adults

the neonatal research network was doing

a study a factorial design of

hydrocortisone

and dopamine

infants were screened

0 were enrolled which was not good

the issues included eligibility and

consent

but as a secondary issue the real

problem was about what did low blood

pressure mean in a neonate so

how was the blood pressure measured in

the neonatal intensive care unit

have these methods been standardized or

validated in this population

what is a normal neonatal blood pressure

at a given gestational or postnatal age

and the answer was that there were no

normals what is a different definition

of hypotension is it just the number

is it tissue perfusion is it shock is it

lack of urine output

what is the clinical endpoint in the

treatment of hypotension and how is this

endpoint measured so all these questions

came up from a very simple question of

was dopamine going to increase the blood

pressure and at the end of the day it

appeared that dopamine actually was not

effective in increasing the blood

pressure in any of these measures so

quite interesting

this is a slide which is very

interesting about reliability of height

measurements this is a very simple study

looking at different ways of measuring

the height of children in an office

setting so they use stadiometers

rulers and a wall chart

and you can see the problem here is that

the stadiometer

did a really nice job of measuring what

we are hoping is the accurate height of

the child but

the wall charts which are commonly used

in pediatric practice show values all

over the place so if youre trying to do

a clinical trial and youre relying on

an outcome measure of height you have to

make sure that you know how its being

measured and that youre training the

people who are doing the height

measurements to actually measure the

outcome measure accurately

okay

this relates to dosing

but i wanted to make mention of the fact

that frequently with

pediatric studies there are

there is a lack of oral pediatric

formulations that are swallowable

palatable

and that have dosing accuracy for very

young children

and these are a few examples that weve

encountered during some of our trials

the first one

is a split tablet of baclofen

we had a clinical trial of baclofen uh

the tablet strength in the united states

is 0 milligrams the tablet is not

scored so if you cut it in half youre

not going to get half of the drug

substance in half of the tablet which is

a little known fact so if the tablets

not scored you cant cut it in half and

get half the dose because the the active

compound is not ac

dispersed within the tablet

uh in the upper right hand corner is an

accutane capsule so accutane is used as

standard of care for children with

neuroblastoma

unfortunately the peak age of

neuroblastoma is two years of age and

twoyearolds cannot swallow these

capsules

so they have to be chewed or squeezed

onto food the problem is that the

chemical substance in accutane is

cis retinoic acid which isomerizes

in light to all trans retinoic acid

so in other words if you decide to

squeeze it onto food and its sitting in

light its probably the patient is not

actually getting the drug compound you

want them to get

third example is hydroxyurea

the national heart lung and blood

institute has been doing a trial for

several years looking at the effect

efficacy

of hydroxyurea for children with sickle

cell anemia

the issue here is that

the most recent trial the baby hug trial

was dosing children

nine months of age to months of age

so in addition to the dose being wrong

no nine month old could possibly swallow

one of those capsules and so the drug

had to be reformulated into a liquid so

there are many formulations problem its

something to keep in the back of your

mind when youre starting on pediatric

drug development you need to come up

with a product that can actually be

taken

by the child

now that answers the swallowability

problem and the dose accuracy problem

the other issue is palatability and

thats one of those terms that doesnt

have a clear meaning

but i suppose if you could get the child

to take it more than once that would

probably answer

the palatability question

so i wanted to give you a concrete

example of a drug development uh program

and i wanted to talk about maripenum

maripenum is a broadspectrum carbapenem

antibiotic its labeled for complicated

intraabdominal infections in patients

older than 90 days of age the labeling

gap

is in premature infants neonates and

infants less than 90 days of age

we received a written request that had

been declined by the

new drug application holder

and uh the main question was a safety

question is maripenum associated with an

increased incidence of seizures in

neonates there was some indication that

imipenem another drug in that drug class

did increase the incidence of seizures

so the question was was this a problem

in maripenum as well

okay this is a picture of about a 00

gram

very sick

intubated

neonate in the intensive care unit just

to frame

what the issues are with treating

premature neonates of this size

so in terms of the study plan there was

agreement with fda on the use of

extrapolation for efficacy making the

assumption that these severe complicated

intraabdominal infections were similar

to neonatal

or neck excuse me necrotizing

enterocolitis

we were directed to perform dosing and

safety study in the offlabel population

which were divided into four populations

less than weeks of gestational age

again 0 weeks being full term

and postnatal age

less than days

group less than weeks gestational

age and postnatal age to 90 days

greater than equal weeks gestational

age postnatal age less than days and

greater than or equal to weeks

postnatal age to 90 days

okay so problem number one was the

formulation the label dose for adults or

for people older than 90 days of age was

0 milligrams per kilo

so if you have a premature infant

weighing 00 grams

0 milligrams per kilo times 0 kilos

is 0 milligrams we have a 00 milligram

vial that now requires a to 0

dilution

but the solution must be very highly

concentrated to avoid fluid overload in

these children so this was problem

number one is getting the dilution

accurate so that the children were

getting an accurate dose

second problem

is how to do a pharmacokinetic study so

a neonatal blood volume is 0 milligrams

per kilo times 0 kilos is 0 ml so

its a very very tiny blood volume of

this child

we minimize the blood draws by using

sparse pk sampling and also using

scavenge samples so in other words

using samples that had been left over

that had we had times on them from when

the samples were drawn but they were

would be discarded and so we used them

to run the pk samples as well

the assays so the goal of the

drug dosing was to provide matching

exposure and time over the

minimum inhibitory concentration or mic

for each age group

and the goal specifically was to have

the concentrations greater than

micrograms per ml for 0 percent of the

dosage interval and greater than

micrograms per ml for greater than or

equal to percent of the dosage

interval

this is to cover for the gramnegative

uh bacteria that would be covered by

maripenum the drug assays needed to be

highly sensitive and accurate using

extremely small volumes of blood less

than 0 microliters

the dried blood spot method

was developed and crossvalidated with

the plasma assays so in the future if

people are doing pharmacokinetic studies

on maripenum they can just move to dried

blood spots

rather than having to draw blood

and it must be performed according to

fdas good clinical practice guidance

because this data was going to fda and

the fda would be auditing the labs

in terms of serious adverse events these

are right from

the code of federal regulations serious

events include death lifethreatening

adverse events hospitalization or

prolongation of existing hospitalization

persistent or significant disability a

congenital anomaly or birth defect

but we were very interested in one

safety question about seizures

the incidence of seizures in the study

was five percent but the question that

we needed to know was

what is a baseline incidence of seizures

of premature or

any infant in the neonatal intensive

care unit

and so we spoke with the people at

pediatrics who

have contracts with many nicus in the

united states to find out what their

baseline rate of seizures were in that

population and their seizure incidence

was five percent so this was extremely

useful to have this database data as a

background

okay in terms of

uh the infrastructure that it took uh

the number of patients uh to perform

this study was 00 so 00 premature

neonates

and the number of sites sites so in

other words to do this study which was a

relatively simple study took sites so

this is not its very difficult to do a

single site study

so i just wanted to point out the

timeline of basically 0 years here

so the written request went to the nda

holder from fda in 00 it was referred

to nih in 00

we went through some negotiations with

fda in 00

the request for proposals the contract

posting went out in 00 the contract

was awarded the following year first

patient enrolled in 00

last patient enrolled

actually pretty quickly it took about a

year and a half to enroll all those

children

the clinical study report submitted to

fda in 009

the federal notice of the open docket i

will not go into any discussion about

this

was in 0 labor negotiations between

fda and astrazeneca took place at the

end of 0 and the label change was

made in 0 and this is the

maripenum label which you can find on

dailymed the national library of

medicines cache of

drug labels fda drug labels and you can

see that

there are differences in dose and dosage

interval depending on the maturity of

the child

now id like to talk now in terms of

just some generalities about needs for

pediatric drug development plans number

one you need a clearly defined question

you need a feasible pediatric study plan

availability of required resources

including site infrastructure you need a

study design team a clinical team

a lab with very good facilities that can

perform gcp lab quality

assays

and you need a pharmacy

you need eligible pediatric patients you

need if you can find it

the ability to leverage background and

normative data so that you know what the

baseline rate of the disease is

in order to see that theres a change

with your therapy and you need good

communication with the fda

okay in terms of the feasible study plan

uh

generally it its unethical to start a

study that you know you wont be able to

complete

um there was a

funny quote by a man named louis lasagna

who is a pediatric clinical

pharmacologist

called the lasagna rule the incidence of

patient availability sharply decreases

when a clinical trial begins and returns

to its original level as soon as the

trial is completed and you will find

that this is the case

the other thing id like to mention is

that theres an impression that the

international classification of disease

billing codes somehow equal the disease

incidence or the number of eligible

patients this is not correct

so if youre

trying to get an idea of how common the

disease is

the icd9 codes will not be the way to

go there

this is another indicator that studies

are not being completed in pediatrics so

this was a really interesting paper

called clinical research involving

children registration completeness and

publications

they identified all closed pediatric

trials on clinicaltrialsgov which had

been funded by the nih

and the resulting publications from

nihfunded studies from 000 to 00

and what they found was there were about

00 closed studies but only 9 of the

completed studies were published and

this indicates that there is a problem

there is a feasibility problem with

these pediatric trials which hopefully

will be

improved as time goes on

so again in order to start your

pediatric drug development plan you need

a clearly defined question and just to

use the the maripenum case does

maripenum have an increased incidence of

seizures compared with imipenem

and the sub question is what is the

baseline incidence of seizures and

neonates

in the nicu and how can we find that out

and the second question is how are

seizures diagnosed in the nicu

and does the fda review division agree

with the diagnostic criteria so again

going back to the fda and having a

conversation about your drug development

plan

the outcome measures have they been

validated are they agreed upon by the

medical community and the fda

if you were using a biomarker it must be

validated in your pediatric population

it doesnt mean that its an fda

approved validated biomarker but you

should know whether the drug the

biomarker has been validated in children

now clinical these are generally

clinical trials for small populations

so

its important to use a clinical trial

trial design

for small populations to consider

published data as background or to

incorporate pharmacokinetic priors for a

pharmacokinetic sampling strategy its

also important again important again to

have

observational or natural history study

data

if you can as a baseline

its important if you can again to

leverage database data not every

question must be answered with a new

clinical trial some data cannot be

collected in one clinical trial and

database or other observational data can

provide useful supplemental or normal

value data

in terms of infrastructure

there are specific

elements of infrastructure that should

be included in your clinical study team

as well as institution

you will need a pediatrician or a

pediatric subspecialist who understands

the complexities of the question youre

asking you will need a pediatric

clinical pharmacologist in order to

design the pharmacology aspects of your

drug trial

you need an assay development team a

pharmacometrician to do the

pharmacokinetic analysis a statistician

a study nurse coordinator

and someone from your pharmacy

department in order to make sure that

the drug is available

in terms of institutional support you

must have institutional support to

support your recruitment effort

to provide space for patient evaluation

evaluation and procedures

data monitoring regulatory support for

fda submissions

as well as regulatory support if fda

audits you

and as a piece of closeout advice i

found this over the years that when

studies close

typically the materials for the study

are all over the place it would be

hugely helpful to place all consent

forms case report forms related to

inclusion exclusion criteria

primary outcomes and assay validation

and one locked location for future fda

audit in summary pediatric drug

development is complex each age group

has its own complexities the adult

outcome measures may not translate into

the pediatric population

and pediatric drug development requires

a team approach and institutional

support to succeed

and all of these are necessary to

move from the

former feeling that

childrens participation in research is

not ethical

to legislative and practical attempts to

assure that its not ethical not to

thank you so much for your attention

this is dr ann zycheck if you have any

further questions please feel free to

contact me thank you