were excited to have dr peter waldron
pediatric hematology oncologist and a
medical officer in the division of
pharmaco village vigilance in the office
of surveillance and epidemiology at the
center for drug evaluation and research
at the fda
he joined the fda in 00 prior to that
he was in the department of pediatrics
at the university of virginia for 0
years
he received his md degree from jefferson
medical college in philadelphia he
completed his pediatric residency
training
at the medical college of virginia
virginia commonwealth university in
richmond and his hematology training at
the university of washington fred hutch
cancer center in seattle were very
excited to have dr waldron give todays
presentation
welcome and good afternoon to everyone
joining us for todays presentation
my name is peter waldron i am a

pediatric oncologist and im a medical

officer in the division of

pharmacovigilance

im excited to present to you an

introduction to postmarketing

drug safety surveillance

i organize the talk into the following

sections first i will discuss the fda

and where the division of

pharmacovigilance fits into the big

picture of drug regulation

next ill describe postmarketing

surveillance spontaneous adverse event

reports

and the fda adverse event reporting

system which is frequently

shortened to the acronym fares

i will then discuss

then cover case reports and signal

detection

in the interest of time i will skip

development of a case series and

evaluation of a safety signal

and finally i will describe

communication of

safety findings

eftas organization consists of the

office of the commissioner

and four directorates

overseeing the core functions of the

agency

these are foods and veterinary medicines

medical products and tobacco

global regulatory operations and policy

and operations

the center for drug evaluation and

research or cder

is housed under the domain of medical

products and tobacco

the talk today will focus on drug safety

activities within cedar

cedar should not be confused with c burr

as you can see to the left on the slide

thats the center for biologics

evaluation research

and i will not be discussing cedar c bur

excuse me any further

taking a closer look at cedar there are

these are six of the main offices that

perform an essential public health task

by making sure that safe and effective

drugs are available

with support from the other officers

listed on this slide the office of new

drugs

regulates overthecounter and

prescription drugs

including biological therapeutics

the office of generic drugs oversees

generic drugs

cedar covers more than just medicines

for example

fluoride toothpaste antiperspirants

dandruff shampoos and sunscreens are all

considered drugs

the drug safety activities and

surveillance discussed today take place

in cders office of

surveillance and epidemiology

[Music]

or sometimes known by the acronym osc

this slide displays the organization

organizational structure of ose

and the main divisions and disciplines

that work to fulfill

our drug safety missions

in the bottom row

the divisions of pharmacovigilance and

epidemiology

fall under the office which is within

lse

the office of pharmacovigilance and

epidemiology

the naturally the abbreviation ope

i will discuss that further on the next

slide

the other divisions within the office of

surveillance and epidemiology

are medication error prevention

and risk management

the fda frequently uses abbreviations as

youve already gotten the impression

and going forward rather than say

division of pharmacovigilance i will

probably use the abbreviation

dpv

looking more closely into the office of

pharmacovigilance and epidemiology

dpv and the division of epidemiology

monitor and evaluate the safety of all

marketed drugs

and therapeutic biologics

and they recommend regulatory action as

appropriate to protect the public health

our multidisciplinary teams

consist of health care professionals

and epidemiologists with a wide range of

expertise

who focus on drug safety

you can see from these smaller

boxes here

that the

divisions are organized into teams

based on

organ systems or what may be also think

thought of as disease groups

so what is pharmacovigilance

well the world health organization

defines pharmacovigilance as the science

and activities

relating to the detection assessment

understanding and prevention of adverse

effects

or any other drug related problems

examples of other drug related problems

include

a person who re receives the wrong dose

of a drug

a person who receives a drug

by way of the wrong route for example

somebody who receives medicine into

their spinal fluid when it was intended

to be given intravenously obviously the

wrong route

drug interactions

name confusions

including labeling confusions

and evaluation of known risks with

regard to the need for risk mitigation

strategy

beyond that which is included in the

safety information

this evaluation of the need for uh

additional risk mitigation strategy

goes by the acronym rems which stands

for risk

evaluation and mitigation strategy

pharmacovigilance includes the

assessment of a need for such a strategy

now this is our first challenge question

the major responsibilities of the

division of pharmacovigilance include

detecting safety signals evaluating the

safety of drugs and therapeutic biologic

products

recommending regulatory actions

communicating relative relevant safety

information

and im sure all of you

are paying attention and can easily

determine that the answer

to this is all of the above

so why does dpv exist

well one answer uh is provided by this

publication uh that appeared in the

journal of the american medical

association in 0

the investigators who reported these

findings looked at all drugs approved by

the fda between the years 00 and 00

they gathered major regulatory safety

events

that occurred following marketing

approval

they defined a major regulatory safety

event

as a withdrawal of a drug for marketing

of a new boxed warning

or an fda safety communication

as you can see from the slide almost one

third

of the new drugs or therapeutic

biologics

approved during this 0year period had

at least one of these major safety

events

this high frequency of postmarket

safety events

highlights the need for continuous

monitoring

of the safety of novel therapeutics

throughout their life cycle

and that is why dpv exists

who are the members of dpv

dpv is comprised of safety evaluators

and medical officers

who work together closely to carry out

the mission of dpv

the activity

of the safety evaluators include

reviewing

fares medwatch submissions that come in

each week

monitoring other data sources such as

the published literature

and programs to facilitate data mining

affairs reports

preparation of reports for

pediatric advisory committees which are

required to review all drugs that have

an indication which is to say

a

an approval for use

in the pediatric age group

and this is done on a periodic basis

reports to the compounding advisory

committee

responses to citizen petitions

as well as

responding to inquiries

from

congressional members congressional

committees

and

the media in general

in addition safety evaluators prepare

written reviews in response to requests

from

the office of new drugs and others

and

they evaluate and write reviews of

safety signals

that they themselves have detected

the safety evaluators also attend

meetings convened during the evaluation

of new drugs or therapeutic biologics

for the purpose of sharing results of

fda analysis of the application

prior to their approval for marketing

medical officers responsibilities

overlap considerably with the safety

evaluate evaluators

but in addition they provide a

broader clinical expertise

in various uh therapeutic areas

especially dermatology oncology

neurology

nephrology cardiology and others

they also collaborate with the office of

new drugs on safety evaluations

so what does dpv do in their

performance of their duties

based on the pharmac

pharmacovigilance definition and our

placement within the office of

surveillance and epidemiology

this slide details the major

responsibility of the division of

pharmacovigilance

the overall goal of the

cabinet department in which the fda

resides the

department of health and human services

is to advance public health

bpvs role in this mission is to

evaluate the safety of drug and

therapeutic biologic products

we do this by detecting and analyzing

safety signals from all available data

sources utilizing evidencebased methods

this is done by routine

drug safety surveillance and targeted

monitoring

of identified safety issues

in the postmarketing setting including

identification of reporting trends

possible risk factors for adverse events

possible

populations at increased risk relative

to the general population

and other clinically significant

emerging safety issues

we collaborate with other divisions

within

fda including

the groups that ive already mentioned

the division of epidemiology

medical error prevention and the

division of risk management depending on

the safety issue

we recommend appropriate regulatory

action

including labeling changes

risk evaluation mitigation strategies or

rems

and other means to improve

drug safety

finally we communicate the relevant

safety information

through the fda and the medical

literature as appropriate

and now our next challenge question

true or false

safety data is only collected during the

later phases

of the clinical development program for

a medical product

for those who answered false you are

correct

safety data collection is not limited to

the later phases of the clinical

development program

now i will discuss the oops

the

science and principles of post marketing

surveillance

safety data collection is not limited to

the later phases of the clinical

development program

but before we discuss postmarketing

safety surveillance

we need to review premarketing safety

and safety in the overall life cycle

of fda regulated regulated drug products

safety is addressed in all aspects of

the product life cycle

prior to drug approval safety is

evaluated throughout the phase to

phase

clinical trials in conjunction with the

dosage and efficacy evaluations

following drug approval safety

surveillance continues

in the postmarketing setting with a

variety of data sources

a critical part of the overall safety

evaluation

is the entire period

so a critical part of the safety

evaluation during the entire period of

product development

and following product approval

is the implementation of strategies and

actions

to minimize the risk of these identified

safety concerns

in the next few slides i will go over

some of the differences between

premarketing

and post marketing safety information

although premarketing clinical trials

are the gold standard to determine

safety and efficacy

at the time of drug approval

there are limitations to clinical trials

first the size of the patient population

studied is limited

therefore only adverse events that occur

somewhat commonly will be captured

for example drug induced liver injury

is a serious and possibly

lifethreatening reaction

but it is typically rare

thus for an event which occurs

once in every 0 000 patients

clinical trials with even a few thousand

patients

may be too small to identify this risk

also

a demographically narrow patient

population is often included

thus drug interactions or adverse events

that are more common among

underrepresented members of the

population

for example the elderly will not be

captured in clinical trials

also

children and pregnant women are rarely

included

in the initial clinical trials prior to

approval next narrow indications

are usually

the

starting point for drug development

that means that patients are excluded

with

who have

comorbid conditions

therefore the real world population

may look quite different from the

clinical trial population

finally trials typically have a short

duration

and they may not be reflective of a

drugs chronic or longterm use

therefore the trials may not identify

safety concerns that may only occur over

that long time

host marketing monitoring allows for

identification of low frequency

reactions

identifying

adverse events in highrisk groups

identifying drug drug and drug food

interactions

postmarketing safety may identify

a broader spectrum of a reaction

that was identified glory during the

clinical trial

and the breadth of that spectrum may

include

a more severe reaction than was seen in

the clinical trial

finally

post marketing reporting

is a direct line of communication

between health care professionals and

consumers

and the fda

this figure

summarizes a broader perspective of

constructed clinical groups

from randomized clinical trials to case

series

and these groups can inform safety

issues

it contrasts

with the ability to detect rare outcomes

which is directly related to the size of

the population under observation

im going to start this over but

this figure gives a broader perspective

of constructed clinical groups who can

inform safety issues

it contrasts the ability to detect rare

outcomes

which is directly related to the size of

the population under observation

with the confidence in a causal

relationship between

the drug exposure and the adverse event

an important component of causality

assessment

is related to the similarity or

differences

of the comparative group

relative to the treated group

which

that now our next challenge question

which of the following are types of

postmarketing surveillance

spontaneous or voluntary reporting of

adverse events

postmarketing studies

phase one clinical trials

or

selections a and b

the answer is d

because phase one trials

are generally performed prior to market

approval

now that we reviewed the advantages of

post marketing monitoring

this list gives you a sense of the range

of postmarketing surveillance data

sources

first spontaneous or voluntary reporting

of adverse events

cases worldwide can be submitted to

pharmacovigilance databases

such as

the fda medwatch reporting system

also published in scientific literature

publications in scientific literature

for example case reports and

metaanalysis are sources

however these are passive surveillance

efforts

since the reports are only received not

sought or solicited

second postmarketing studies

these studies can be voluntary or they

can be required by fda

types of studies include observational

studies including those that use

automated healthcare databases

or even randomized clinical trials

a different type of surveillance is

fdas sentinel system which uses health

insurance claims databases

to identify clarify or strengthen

drug related safety concerns

above i describe the medwatch program as

a passive surveillance system

as you may guess there are also active

systems

examples of active systems include the

drug

drug induced liver injury network

abbreviated as dylan

which was developed to identify and

enroll cases of drug induced liver

injury

these efforts to develop the network

identifying enroll cases

report and analyze the cases

all represent an active surveillance

process

other active surveillance databases

which use developed networks to detect

events of interest include

the nice cades system and thats the

national electronic injury surveillance

system cooperative adverse event drug

event surveillance project

this is a project of the centers for

disease control

and

another active surveillance system is

the national poison data system

to which regional poison centers submit

their data

we will now focus on post market adverse

event reporting

a key aspect of post marketing safety

surveillance

and how you

as healthcare providers

can participate in pharmacovigilance

but first

our next challenge question

which of the following countries does

not require practitioners

to report adverse events to a national

registry

france norway

sweden the us

the correct answer is d the us

in the united states there is no adverse

event reporting requirement for

practitioners

this slide explains how voluntary

adverse event reports are submitted to

fda

two pathways exist

for patient consumers and health care

professionals to report

a suspected adverse event

first the reports can be submitted

directly through fdas medwatch program

which encompass approximately five

percent of all reports

though this estimate fluctuates every

year

these are then referred to as direct

reports

alternatively

reports can be submitted to the product

manufacturer

who is then required to submit all such

cases to fda

it is through this route that the vast

majority of cases are received

into the fda adverse event reporting

system fairs

under the code of federal federal

regulations uh cfr 0

post marketing safety reports must be

submitted to fda

for the following circumstances

first expedited reports

must be submitted when an event is both

serious and unexpected

adverse experience from all sources both

foreign and domestic

must be submitted as expedited reports

you may encounter

the acronym

relative relevant to this of

susar or susar

and thats simply the abbreviation of

suspected

unexpected

serious

adverse reactions

expedited reporting means

that a manufacturer is required by law

to submit

those

sasar cases cases

within days of their receipt of the

information

all other reports are required to be

submitted

on a

nonexpedited

timeline

these include

reports that are

serious

but expected

uh reports that are nonserious

even though they are unexpected and

reports that are nonserious and

expected

these reports the nonexpedited reports

can be reported quarterly

so they do not need to be expedited they

are reported quarterly for the first

three years and then annually

thereafter

serious adverse events

in this context sirius has a specific

meaning

you may also hear the term regulatory

serious

to indicate that the everyday english

word sirius

is being used with a specific or

technical meaning

that is different from its everyday

meaning

this list of regulatory serious events

is defined in the code of federal

regulations and it is legally binding

the regulatory serious adverse events

are death

lifethreatening adverse experience

inpatient hospitalization which is

either new

or prolonged

persistent or significant disability or

incapacity

congenital birth defects

and others serious

now examples

of other serious would include some

an adverse event such as bronchospasm

in case theres any uncertainty about

what a lifethreatening adverse

experience is

a reasonable example is that of an

anaphylactic reaction in which there are

systemic signs such as breathing

problems or low blood pressure

um in the context of a an allergic event

so that is an anaphylactic reaction

that would be considered a

lifethreatening adverse experience

and now our next challenge question

the incidence of adverse drug events

can be determined through spontaneous

reporting systems

true or false

here its worth pausing to consider what

one needs to know

to define an incidence

from what you know about spontaneous

reporting

does it provide those necessary elements

the correct answer here is false

because spontaneous adverse reporting is

voluntary

one does not know the number of exposed

persons and thats the denominator part

of the incidence

or the true number

who were exposed and developed the

adverse event of interest or the

numerator the numerator for the

incident rate calculation

therefore an incidence of that adverse

event cannot be determined

from

spontaneous reporting

here are some examples of factors that

affect spontaneous reporting

both from consumers and healthcare

professionals

these include media attention

for example in 0

homeopathic teething tablets for

infants who are just cutting teeth

and associated anticholinergic adverse

events

attracted a lot of publicity

following fda communications and media

coverage fda saw increased reporting of

these events

litigation

many of you have likely seen commercials

that advertise law offices

trying to contact patients who may have

suffered an adverse event

one example recently is the direct

acting oral anticoagulants

the seriousness of the adverse event the

drug product and the indication

also can influence whether and how often

an event is reported

there are typically few reports for

overthecounter medications as an

example of this

the number of reported adverse events

for a drug

usually rises during the first few years

of marketing

and then typically declines

even if prescribing rates remain steady

the quality of the manufacturers

surveillance system may also impact

reporting

as large companies have resources to

follow up and engage with persons

reporting adverse events

but smaller or newer companies may lack

these resources

finally regulations affect reporting

particularly in terms of what

manufacturers are required to submit to

fda

for example

overthecounter

monograph products

did not always have mandatory post

marketing safety reporting

then in 00

the dietary supplement and

nonprescription drug consumer

protection act was signed by then

president george w bush

to add safety reporting requirements for

overthecounter drug products

that are marketed without an approved

nda application

the fda adverse event reporting system

is a computerized database of

spontaneous adverse event reports

for human drug and therapeutic biologic

products

it has collected data since 99

and over million reports

are currently stored in fares

with million reports

submitted in the year 00 alone

adverse events are coded with special

terms called nedra med

dra medra terms

to facilitate searching for specific

types of adverse events

the

term medra is an acronym for the medical

dictionary for regulatory activities

this

medical dictionary from regulatory

activities or medra

is updated yearly since healthcare

continues to change

this graph shows the number of adverse

event reports

on the yaxis

entered into fares each year

since

starting in 00 on the xaxis

each bar is stratified by report type

blue and yellow colors represent reports

submitted from manufacturers

while at the top of each bar dark green

colors represent reports submitted

directly

to medwatch

as you can see most reports come from

the manufacturers

and each year more and more reports are

entered into fares

the expedited reports shown as blue bars

are reports that are both serious and

unexpected as we talked about previously

something to consider uh remember

that adverse event reporting is not

required in the us

so should this figure be interpreted to

mean that roughly as many expected

adverse events occur

as serious unexpected or expedited

reports

or

could there be some bias in reporting of

expedited reports

relative to the nonexpedited reports

some people might be noticing that in

0

there was

quite a jump from 0 and wondering

whats going on there well

at that time the fares database was

updated to include

approximately 00 000 nonexpedited

reports containing data from previous

years

this was a database

correction

not a true reflection of increased

reports

for the calendar year 0

fares is a drug safety surveillance tool

with many strengths

it includes all us marketed products

and may include farm products fares

includes all uses both approved

indications and offlabel uses

for example if a drug was only approved

for

schizophrenia

it may also be used for

patients with bipolar disorder or

depression

and those events those any adverse

events that occur in that population

will also be

included in fairs whereas a clinical

trial

that

only included schizophrenic patients

may see a slightly different profile of

adverse events

fares also includes a broader patient

population which

includes all age groups

that

for example children who may receive a

drug as well as the elderly whereas

those people may be excluded from

the clinical trials prior to approval

it also may include

women who are pregnant and patients who

have

comorbidities

who may be excluded from clinical trials

fears does have important limitations

though

and these are described on the right

side of the slide

fares

may capture events which represent

worsening of preexisting disease

or a worsening of a comorbidity

that happened to occur simultaneous with

the initiation drug

and

affairs in general

is not highly capable of distinguishing

that event from an adverse

drug event

the quality of the fairs reports can

vary greatly well talk about that

further on but that can be an important

limitation of

fairs cases

it is not possible to estimate the

incidence as weve already talked about

and that is both a numerator or event

detection problem as well as a

denominator or exposure

population problem

adverse events that could be

manifestations of the disease for which

the drug is indicated

some

diseases have a broad variety of

manifestations

that may not be appreciated initially as

being related to the disease

and they may manifest themselves

simultaneous with the initiation of the

drug

and so those can be difficult in the

context of

a report on a piece of paper or on a

computer screen relative to the

assessment of that person who is in

front of you as

a clinician has available to determine

that

fears is ideal though for adverse events

that are rare

that is events with a low incidence in

your general population

such as acute liver failure

serious skin reactions such as

stevensjohnson syndrome

or progressive multifocal

leukoencephalopathy

often abbreviated as eml

this is an infectious disease that

occurs with specific aspects of immune

compromise

fares is more useful for adverse events

that occur shortly after exposure

rather than after a long latency

and for identification of events

for which clinical trials may have had a

blind spot

this blind spot could have been

developed

because a atrisk patient population was

not included

or monitoring

for that particular adverse event was

not part of the clinical trial protocol

as well as for other reasons for which

clinical trials may have blind spots

i discuss where safety information comes

from and what constitutes a safety

signal

now i will discuss how you can report an

adverse event to the fda

through the medwatch program

there are two ways to report to medwatch

online at the website listed

or the forms can be downloaded from the

site completed and then mailed or faxed

to fda

the midwatch program allows for easy and

convenient reporting

of suspected adverse events the fda

when you log into medwatch to report an

adverse event

youll be walked through an electronic

questionnaire

in 0 fda released a medwatch form

designed specifically for consumers

the form called the medwatch 00b

is shown on this slide

although there are multiple questions on

the form

four questions must be answered

in order for the report to be accepted

there must be a patient

a product an event and a reporter

of course we encourage reporters to

include all the pertinent information

on these forms

and that the previous slides summarized

the consumer form contains the same

primary component of the medwatch as the

00 form

but it is written at a reading level

intended for the general public

input from consumer advocacy groups and

the general public was considered when

developing the form

reporting adverse events for brand

versus generic products

manufacturers of brand name sometimes

referred to as the innovator product

and generic products have identical

regulatory obligations to report adverse

events

innovator manufacturers generally submit

the vast majority of adverse event

reports

even after generic approval

this indicates that familiarity of

patients and providers with brand names

leads to preferential reporting to

innovator manufacturers

this can make determination of adverse

events that may be specific to

a generic product

difficult to sort out from

those events that are occurring due to

the active ingredient which is present

in all of these forms

the pharmacovigilance of biologic

products

presents a unique challenge due to

naming conventions

this is a relatively recent development

because its only recent that we have

had

other than the brand name or innovator

versions of biological products

examples of these include

the nonproprietary name of phil graston

the trade name neupogen

and now with the uh availability of

biosimilars or

generic versions of biological products

there was a need for an additional

naming convention which

resulted in the addition of the four

letter uh

suffix to

the

active ingredient name and so we have

the

biosimilar

phil graston sndz

and the biosimilar filgrastim aafi

now the hope is that when there are

adverse event reports that

the reporters will use the suffix the

four letter suffix

to specify uh the biologic product for

which the adverse event is being

reported

and now well talk about the uh

aspects of a good case report

pharmacovigilance at cedar depends a

great deal on spontaneous reporting

and so

going into the details of this

is useful

well start out with

a what might be called a straw man

so

a health care worker reported a male

patient started drug x

at five milligrams daily for type

diabetes on february 0

on an unknown date the patient developed

liver failure

additional information was not provided

now

this is not a

an exaggerated case

this is a case that is um quite common

uh with regard to this level of detail

and

as you can tell

this case is acceptable

because it has the four required

elements that i mentioned earlier it has

a patient a drug an adverse event and a

reporter

but there are

details missing

um its missing

the temporal relationship

between

the start of the drug and the adverse

event

its missing

any consideration of possible

alternative causes

such as

comorbidities or concomitant medications

and therefore the ability to

have confidence in

the relationship between the drug

exposure and the event

either cannot be evaluated which would

be my preference and interpretation

or

some might say that its possible but

undeterminable

so a not a high quality case for those

reasons

a second case

which

might be included

as a star case or a best representative

case

is described here

9 year old male type diabetes with a

so this is our past medical history part

type diabetes hyperlipidemia

hypertension

and explicitly no history of liver

disease

the patient started drug x on february

0

the concomitant or other medications

given simultaneously were simvastatin

and lacinopril

also

importantly

these findings of baseline laboratory

values were

are reported on the same date as the

start of the drug and they were normal

the patient an important negative and no

alcohol use which suddenly could

confound evaluation of

a liver toxicity

and then

eight weeks so we have a timed onset of

the event eight weeks after starting

drug x the patient presented to the

emergency department with a fiveday

history of jaundice dark urine and

nausea and vomiting

he was admitted to the intensive care

unit and was subsequently diagnosed with

acute liver failure

drug x was stopped on admission

evaluation of viral hepatitis was

performed and

that alternative cause for

the acute liver failure was eliminated

with no other intervention and so

no alternative

uh

treatment that might make it more

difficult to determine uh why the

patient got better the only intervention

was stopping the drug

seven days after stopping

the patient had

his lab values returned to normal and

resolution of the acute liver failure

and so

these are the features that make this

a

a high quality case

that allow

the review team to

consider the causal relationship between

the drug exposure and the event

to be likely or

in the

official term that we would use probable

so heres a list of components of a good

post marketing report that allow for

adequate case assessment

the description of the event

the

suspected and concomitant

therapy

patient characteristics including

of the demographic the demographic

features

the baseline medical condition

comorbid conditions

and sometimes of

important relevance family history and

other risk factors

the documentation of the diagnosis of

the adverse event in question

and this is simply the criteria that

would be used

for any diagnosis and so

if somebody is considered to for example

have a myocardial infarction

if you see

[Music]

serum markers

[Music]

of a

cardiac muscle injury

if you see arteriography showing

blockage of coronary arteries um or if

you for example to switch adverse events

say a patient had

thrombocytopenia and so a platelet count

of 0 000 would be an unambiguous

support for that claim uh that

diagnostic claim

so the clinical course and the outcome

what happened to the patient

um

did they get better did they get better

with intervention

did they get worse

the relevant therapeutic measures on

laboratory data

sometimes this is overwhelming

and but

hopefully

a reporter who is being

uh

considerate about the

the relevant data

that theyre not providing extraneous

information

the challenge of me challenge is a

concept that isnt widely known a d

challenge refers to the response to

stopping the drug

and rechallenge is sometimes not

advised but is very informative if it

occurs it refers to

a patient who had an adverse event that

adverse event has resolved completely

and then subsequently the patient is

exposed to the same drug again

these cases

when reported are highly informative

because

they

provide a

situation in which

the person who is living their life

in two different time points

with a lot of other things being

different as our lives are

life goes on

but what is the only common thing that

preceded the adverse event

is the

uh drug exposure and so

with rechallenge if the same adverse

event occurs

that is highly suggestive

of a drug

causal relationship to the adverse event

the reporter contact information uh we

do uh reach out to reporters uh for uh

additional information at times

uh were less successful uh were

successful less frequently than we would

like to be with getting

responses but sometimes those are very

important and very helpful

and then the miscellaneous so

those are components of a good

postmarketing report

the next few slides will define safety

signal

fares is a large database

and it is often difficult to find

uh safety signals within that database

and so after defining a safety signal

well discuss how we can optimally

manage

these data

there you go

so but first another challenge question

um a new safety signal could be

um

a new previously unknown adverse event

a new drug interaction

an adverse change in quality sorry in

quantity severity

or the affected population of a known

adverse event or all of the above

and the correct answer is the

all of the above

so

on the left um are

some possible definitions

of

a safety signal

and

in reality

a safety signal is a hybrid or

an aggregate

of these definitions

so safety signals are reported

information that describe a possible

not proven possible causal relationship

between an adverse event

and a drug

and the relationship is previously

unknown or incompletely understood

on the right side are examples of

signals these include

new adverse events drug interactions new

adverse risk populations

or greater severity about a known event

an example of greater severity

is an adverse reaction of transient

elevations in

serum liver associated transaminases

an example of a greater severity would

be a signal of fulminant

or

acute and lifethreatening hepatic

failure

another example of a safety signal

involves the previously marketed drug

raptiva or ap tiva

that is the trait name for a drug

that was marketed

for the active ingredient

ethylism

ethylizumab

is a monoclonal antibody directed

against a lymphocyte expressed integra

molecule

it was approved for marketing as a

treatment for psoriasis

however

early in the course of its marketing

an adverse event of progressive

multifocal leukoencephalopathy was

reported

now as we discussed pre previously uh

pml is a rare and usually fatal

demyelinating demyelinating diseases

that causes severe brain dysfunction and

frequently is fatal

pml is an opportunistic infection that

occurs in immune compromised patients

in 00 and 009 three cases of pml were

reported to fares

in patients receiving

ephelismapp

for psoriasis

which is generally not considered and is

generally not an immune compromised

state

in february 009

the fda issued a public health advisory

to notify health care professionals of

those three confirmed

and one possible report of pml

then in april 009

the manufacturer genentech

withdrew raptiva from the market

consistent with fdas recommendation

what is a safety signal

a safety signal has been defined in many

ways by different groups and in varying

contexts

the council for international

organizations of medical sciences

which uh in the us is abbreviated as

science but since its international i

dont know how other people pronounce

that

this organization defines a safety

signal as information that arises from

one or multiple sources

including observations and experiments

which suggest a new potentially causal

association

or a new aspect of a known association

between an intervention and an event or

set of related events either adverse or

beneficial

the beneficial part is curious but keep

that in mind its unexpected thats the

key component

in general safety signals are reported

information that describe a possible

causal relationship between an adverse

event and a drug

and the relationship is previously

unknown or came incompletely understood

this is a slightly uh

brief

and i would call a distilled version of

the scions version

so pharmacal vigilance may include

review of many different sources

of safety signals weve already talked

about sayers

sorry fairs

data mining databases

is another

potential source of safety signals

uh the medical literature

as well as

periodic adverse experience reports

that we talked about earlier

manufacturers are part required

to submit quarterly during the first

three years

of a drugs life

and then yearly thereafter

other sources of safety signals may

include study results from clinical

trials

epidemiologic studies

registries

even the media

the manufacturers global safety

database uh is a source that sometimes

is produced spontaneously sometimes

through inquiry from

dpv and the

fda um occasionally inquiries come from

citizens petitions

and

also

the international regulatory agencies

may identify a safety signal that we

have missed and certainly or had not

seen or had not considered and certainly

that happens

going the other way as well

they are a signal

source

at times

the list of the possible sources of

course continues to expand as new

resources tools and data streams become

available

so

next well

examine some of the uh

sources of safety signals

that we use on a routine basis and this

is

goes under the term of data mining

a principle tool of data mining

is

looking at disproportionality

this is

an important tool

in fairs

because

fairs is um

one of adverse events um and

in order to separate out the adverse

event for a particular signal in

question

from the ocean

of adverse events that exist in fares we

need tools to do that

the data mining method of

disproportionality

helps us to identify trends and

reporting and new safety signals data

mining is a mathematical tool that

identifies

higher than expected reporting frequency

of product or drug event combinations

and this is reflected in various

statistical scores

including um the most common uh score

that we use

which is uh called the eb

0

this uh score

uh indicates

uh

when the value for the eb0 is greater

than or equal to two

a 9 percent confidence

that a drug event combination

appears at least twice

at least two times

the expected rate

when considering

all other drugs and all drug events in

the database

data mining aids in finding reports and

events

that are out of the ordinary or

disproportional

data mining is intended to be

hypothesis generating

and can prompt review

and may supplement the comprehensive

review

in fairs

it does not confirm causality

or replace the clinical review

of case reports

the final step

in the safety analysis that i described

is to communicate these findings

here are two examples of recent drug

safety communications from the fda

however the drug safety communication is

used selectively

to announce safety labeling changes

other means of communicating safety

findings are

the fda website which lists safety

labeling changes

manufacturers may choose to send notices

to prescribers

these are

referred to as dear health care provider

letters

and

dpv and other

office of surveillance and epidemiology

divisions

frequently publish reports of safety

findings in the medical literature

all of these forms of communication are

intended to deliver

these important safety findings to

persons who need to know about them

the previous slide listed empirica

signaling a data mining program

which we apply to the fares database

as one of possible sources for safety

signals

this data mining method

helps us to identify trends in reporting

and new safety signals

data mining is a mathematical tool that

identifies higher than expected

reporting frequency

of product event combinations

and this is reflected in various

statistical scores

including eb0

a

ebo score

of greater than or equal to two

indicates

9 percent confidence

that a drug event combination

appears at least twice

the expected rate

when considering all other drugs

and events in the database

data mining aids in finding reports and

events that are out of the ordinary

data mining is intended to be hypothesis

generating

and can prompt a review

it may also supplement

the comprehensive review of the report

in fairs

it does not confirm causality

or

replace the

clinical review of the case reports

and with that

i thank you for your attention

and

have a good afternoon