hello everyone uh my name is Van mum
Science Center I will today talk about
the pharmacokinetics and
pharmacodynamics of theraputic
products section one of uh the talk will
uh introduce you to therapeutic proteins
the goals of this section are to
appreciate the contribution of
therapeutic proteins to the collection
of approved medications to understand
key structural features of theraputic
proteins in contrast to small molecule
drugs and to recognize the role of
clinical pharmacology Concepts in the
clinical use of therapeutic
proteins this slid shows the FDA drug
approvals from 9 99 to
0 and differentiates between new
molecular entities or nmes shown in blue
as traditional small molecule drugs and
Blas or biologic license applications
shown in Gray biologic license
applications include thetic proteins but
are also for example blood or blood
products as well as vaccines as you can

see over the last couple of years the number of biologic license applications from the overall number of approved drugs has relatively been constant as approximately one quarter so over these uh last years especially uh therapeutic proteins have become a major part of our uh collection of drugs that are clinically used to remind everyone about proteins and protein structures each protein has a unique structure as everyone probably remembers uh you usually have the primary structure based on the amino acid sequence thats shown here on the left side where each letter stands for a specific amino acid in addition to this um primary sequence however you also have a secondary tertiary and quinary structure and this is basically the threedimensional arrangement of this uh linear amino acid chain so perfectly linear amino acid polymer is neither functionally nor energetically favorable uh in the aquous

environment in the body you basically
get uh folding based on these uh uh the
interaction between hydrophilic and
hydrophobic uh moities uh in the amino
acid sequence and by that you get a
defined threedimensional structure and
this threedimensional structure is
stabilized by hydrogen bonding of under
theal interactions uh sometimes
disulfide Bridges so relatively weak
Atomic interactions that uh produce a
defined threedimensional structure that
is necessary for the stability
as well as the function of the
therapeutic protein since this
stabilization is produced by relatively
weak interactions it also means that
therapeutic proteins are usually
relatively susceptible
to uh disturbances from either
mechanical um stress as well as
temperature stress and by that often
times for example require uh
Refrigeration uh to uh for their
storage what I also would like to remind
everyone about is that the theraputic

proteins comprise a large variety of molecular structures so you have structural diversities as an example a small therapeutically used protein is insulin consisting of amino acids and a molecular weight of approximately kilodalton

albumin itself probably not used uh as a therapeutic protein but often times a major part of um Fusion proteins alumin has a molecular weight of kilodalton and consists of amino acids and compared to that a immune globulin G molecule like a monoclonal antibody which has a molecular weight of approximately 0 Kil do and consists of around 00 amino acids as you can imagine the different structure the different molecular weight and the different size of these molecules has also an impact on how they interact with structures in the body how they are handled by the body and how their PK and PD are

affected when we compare traditional small molecule drugs with proteins then

small molecule drugs are defined by chemical structure and Purity we know exactly what kind of chemical structure they have and in what Purity they are available to for example be used as an API in uh producing a therapeutic uh a a therapeutic medication they are chemically synthesized examples so just give me a fental ibuprofen and they are identical from batch to batch so since they are batchwise produced and synthesized these batches if we compare them are uh completely identical with regard to structure and Purity in contrast to that therapeutic proteins are produced in living organisms in either um Maman or uh bacterial cells they are defined by the production process rather than their structure uh chemical structure and Purity so that then means that the production process needs to be extremely carefully controlled it needs to be a controlled environment for these microorganisms as they are usually defined in the chemistry manufacturing

and control requirements the CMC

requirements for a therapeutic proteins

and then these therapeutic proteins that

are produced are usually characterized

with a variety of different socalled

critical quality attributes or

cqa um that can be uh between 0 and 0

to 0 uh different attributes that are

relevant for a large therapeutic protein

like a monoclinal

antibody each product is uh through this

defined production process unique

examples for therapeutic proteins um for

example a delum map as a monoc anybody

or teros cep as a fusion

protein since

these proteins are also produced in

batches in living organisms these

batches are highly similar but they are

not identical simply because of small

variations that may occur within this

carefully controlled environment in

which the genetically modified living

organisms are grown are housed and

ultimately produce uh the therapeutic

protein of

Interest so batches are highly similar

but not

identical when we look at Major classes

of therapeutic proteins that are

clinically used then the biggest one are

probably uh monoclonal antibodies and

antibody constructs so this includes uh

Native IGG molecules uh like bever map

used in cancer indications in flexim map

for treatment of uh rheumatoid arthritis

and other chronic inflammatory

conditions uh then antibody drug

conjugates where a IG molecule is

conjugated with a small uh molecule drug

that ultimately carries its own activity

so the antibody May either be used as a

delivery device only or may also

contribute uh to pharmacologic Activity

one example example is btox viotin used

in lymphoma so this molecule is

obviously then produced not only by a um

production process that is in a living

organism but is then subsequently

chemically modified uh through the

conjugation process with a small

molecule

drag and then we have more recently many

anybody fragments and anybody constructs

that use parts of an i molecule and

combine it in a variety of different

forms and Fashions uh for example uh rib

zum map is uh used as an antibody

fragment in age related macular

degeneration or Blinder tumor map as B

specific anybody derivative uh used in

acute lymphoblastic

leukemia the second big group are

hormones and growth factors which are

usually uh identical or closely similar

to endogenous molecules and uh

supplement or replace a lack of of these

hormones or growth factors an example of

course insulin for type diabetes H

filgrastim as a growth factor for uh

white blood cells uh to treat

neutropenia neutr grow factor and then

beta interferent for the treatment of

multiple sclerosis

the third group are enzyme replacement

therapies where large uh molecules that

are have enzyme activity and that are uh

either dysfunctional or completely

missing in uh specific individuals that
are affected by genetic disorders are
replaced an example for that is aaly
days beta in Fab
disease now luckily the
uh Central Paradigm of clinical
pharmacology that we know from small
molecule drugs is equally applicable to
therapeutic products that means when we
give a dose or dosing regimen to a
patient that results in concentration
time courses in different organs and
tissues that these concentration time
courses are ultimately the driver for
the clinically uh observed efficacy as
as well as potentially Adverse Events or
toxicity and the relationship between
the dose and the concentration is still
uh characterized by
pharmacokinetics and the concentration
effect relationship to the desired as
well as undesired effects is
characterized by pharmacodynamics so we
will in the following focus on the
pharmacokinetics and pharmacodynamics of
pkpd of these therapeutic

proteins

so in summary for this section biologic

license applications constitute

approximately one quarter of the overall

FDA approvals for new medications in the

last 0

years therapeutic proteins comprise

macromolecules of white structural

variety with different molecular weights

and physical chemical

properties therapeutic proteins are

produced in living organisms or cells

and are defined by the production

process rather than the chemical

structure and the same Central Paradigm

of clinical pharmacology holds true for

therapeutic prodence as for small

molecule

drugs here is a self assessment question

regarding the first

section