Biologics or biological drugs

•officially (WHO) „biological and biotechnological substances“

Basic characterisation of biologics

•typically acquired by other way than by classical chemical synthesis (semisynthetic modifications are possible)

•typically M_r > 1000 (up to 1000 „small molecules“) - greater, more complex, usually exhibit a *primary structure* (a sequence of amino acids or nucleotides), a *secondary structure* (α-helix, “folded sheet”, influence of -S-S- bridges), a *tertiary structure* (general space arrangement of a monomeric molecule) and a *quraternary structure* (grouping of monomers); many proteins are glycosylated

•but both above conditions need not be necessarily fulfilled for classification of a drug as a biologic

Some possible problems in terminology

•pharmaceutics = technology of manufacturing of application forms of drugs

("pharmaceutical technology" is the literal translation from Czech)

⇓

•biopharmaceutics ≈ biopharmacy = „a discipline concerning drug absorption" on a frontier of pharmaceutics and pharmacokinetics (pharmacology)

•biologicals: analogy to chemicals ⇒ they include „biological drugs" but also diagnostic monoclonal antibodies, enzymes used in technology etc.

•biologics: the term mostly used for „biological drugs"

⇓

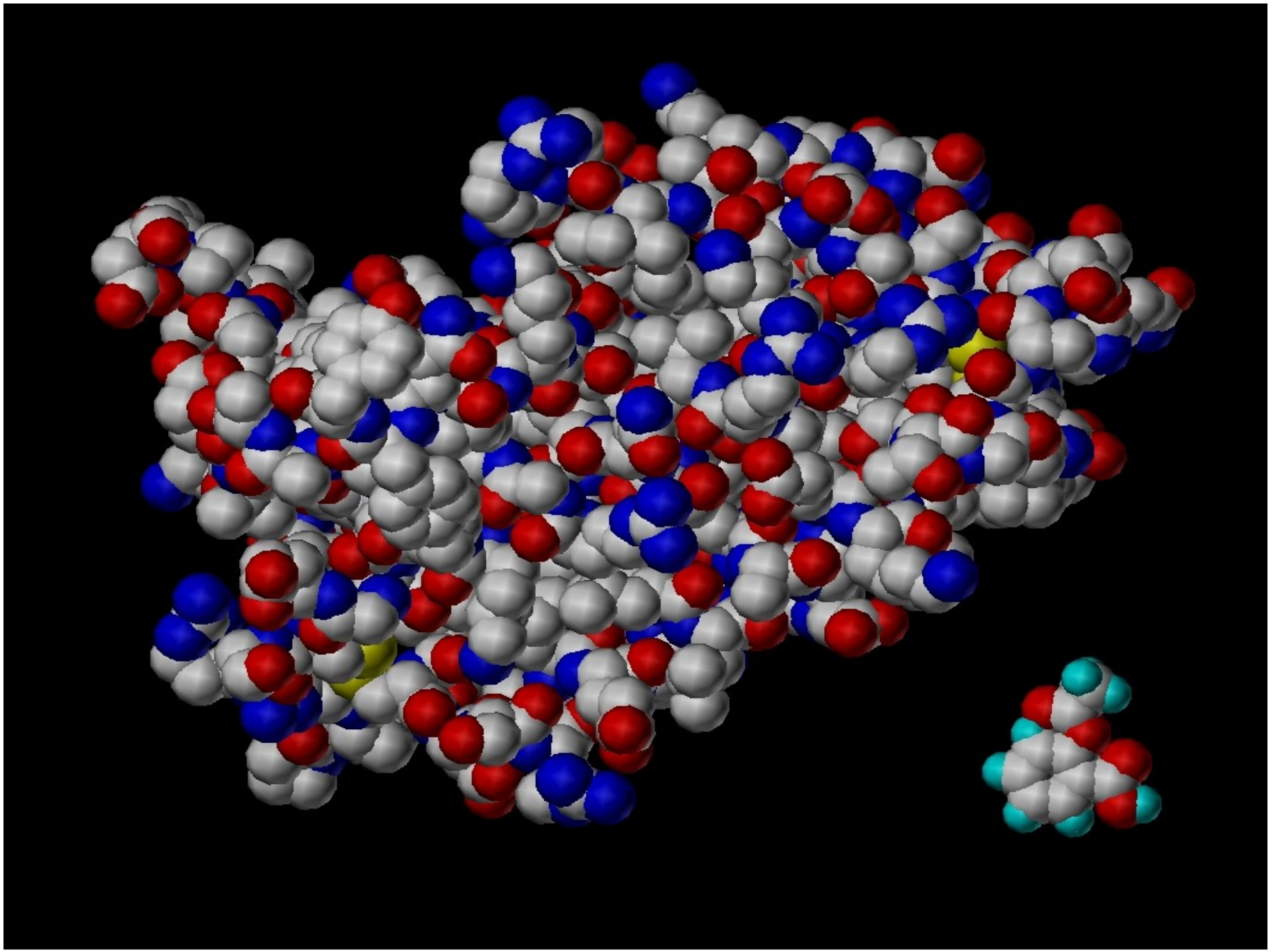
„Biopharmaceutics" is not a suitable name for a subject devoted to "biological drugs", but is also used.

Differences in production of “small molecules” and biologics

•small molecules – classical organic synthesis: chemicals with exactly defined chemical structure and purity react under exactly defined conditions with a predictable and preciously verifiable results

•biologics- preparation by „harvesting“ of compounds produced ancreted by artificially constructed cells (genetic engineering)

An illustration of the difference between a biologic and a “small molecule”
erythropoietin and acetylsalicylic acid

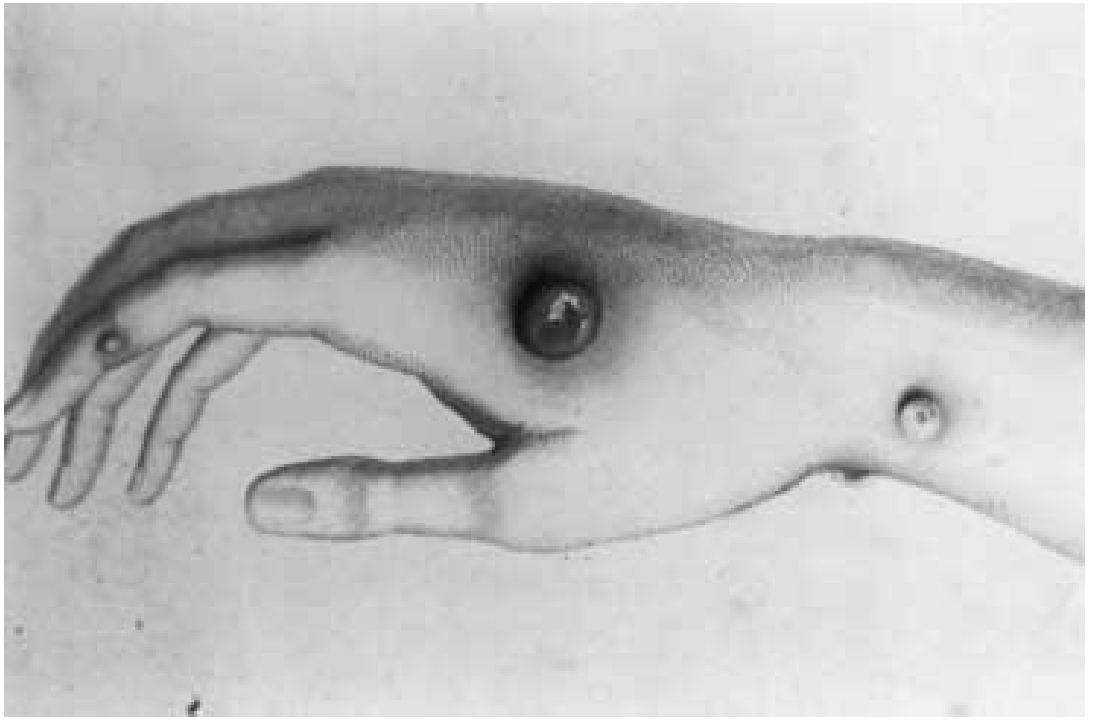


History of biologics

•the Antiquity and the Middle Ages: usage of leeches for treatment of circulation and blood disorders (hirudin)

•classical vaccines: preparation of dead or attenuated bacterial cultures or attenuated or inactivated viruses (e.g. pox: transfer of the infection „from a skin to a skin“ has been known long since around 1000 A.D. in China; 1796 – Edward Jenner demonstrated that putting of the purulence from a furuncle of the cowpox in under the skin protected against the infection with pox; 1805 – 1st vaccine against pox was prepared on the calf skin in Italy; 1864 – mass usage of this vaccine; after 1940 – lyofilized vaccines (Collier))

Edward Jenner. Lithograph based on the painting by J.R. Smith (1801).
Courtesy of the Institute of the History of Medicine, The John Hopkins University,
where the original painting is on display.

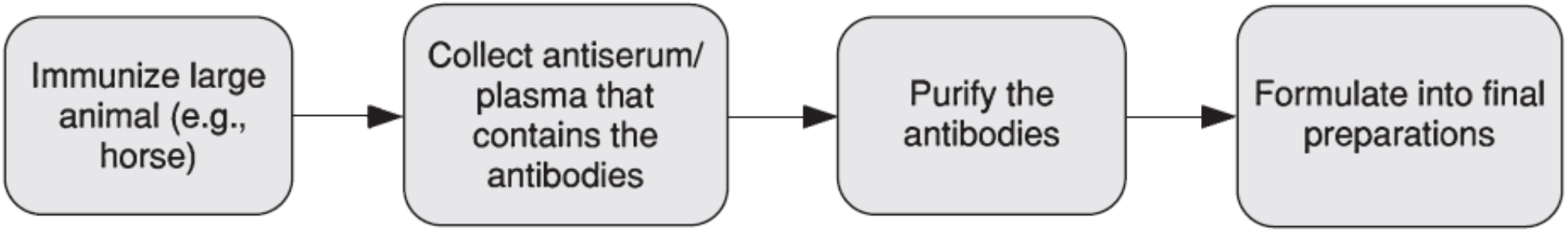


The cowpox lesion on the hand of the milkmaid, Sarah Nelmes,
from which Jenner took pustular material to inoculate the boy James Phipps,
May 1796. Case XVI of Edward Jenner's 1798 report on vaccination (2).

History of biologics - continued

•(poly-clonal) antibodies („sera“) - immunisation of a suitable production macro-organism (eg. horse, rabbit) with a noxious agent (a toxin, e.g. a snake poison), a serum acquired from the blood used as an antidote; monoclonal antibodies for analytic and diagnostic purposes, then a suitable transformation (RIA, ELISA)

•peptides – isolation from biological material (insulin: Banting and Best 1921)

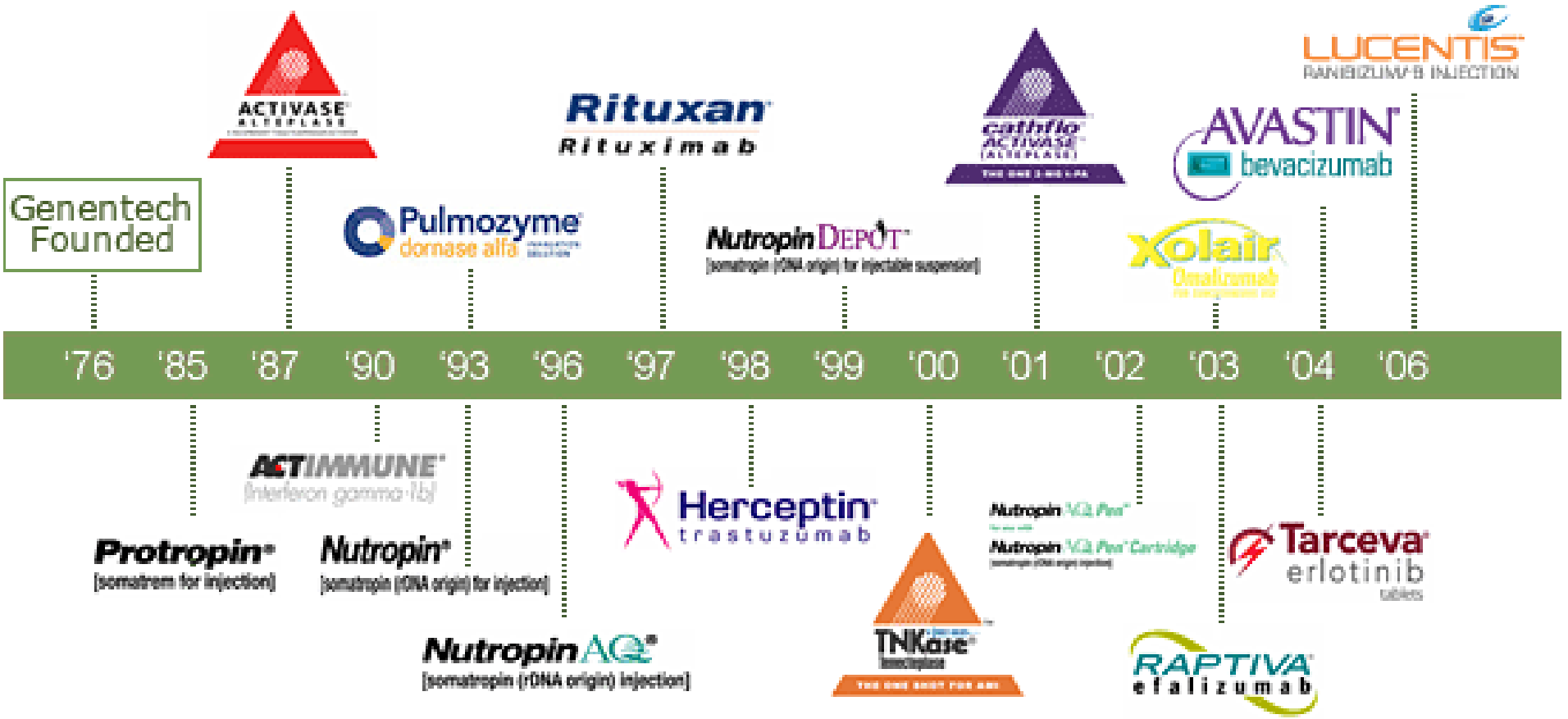


Production of polyclonal antibodies from horse antisera.

More recent history of biologics – genetic engineering

- 1977 - somatostatin first time prepared by a recombinant technology in *E. coli* (Genetech, USA)
- 1978 – human insulin cloned
- 1982 – recombinant human insulin prepared in *E. coli* marketed
- 1984 – Factor VIII of the blood clotting first time prepared in a laboratory
- 1985 – FDA approved somatrem, a somatotropin analogue
- since 1980th – development of therapeutic monoclonal antibodies (mabs)
- in 1980th 80 % of mabs of mouse origin, in 2000th only 7 %
- OKT3 - murine anti-CD3 antibody was the first mab approved by FDA for treatment of organ transplant rejection

History of biologics from the point of view of a corporation (Genetech)



Development and authorisation of biologics

EMA (EU): normal approval procedure like for any other drug

FDA (USA): possibility of taking part into so called Fast Track Drug Development Program (since 1998, revised 2004) – the prerequisite is the usefulness for serious or life endangering condition and legitimated hope for better clinical efficacy than up to the present time used drugs

Generics and „biosimilars“

Generics: small molecules – contain the same active compound as the original and reach 80 – 105 % of the bioavailability of the original

„Biosimilars“ or „Follow-up Proteins“: contain a biologic prepared by the similar procedure and with the similar effects as the original

Different approaches of FDA (USA) and EMA (EU)

- EMA: consistent testing of effects in the relationship to the proposed therapeutic usage; the security of the patient is fundamental; neither generic prescription nor substitution among biosimilars
- FDA: more liberal approach; full support for „biosimilars“ approvals

Committee for Medicinal Products for Human Use (CHMP) Guideline on Similar Biological Medicinal Products

(CHMP/437/04)

"It should be recognised that, **by definition, similar biological medicinal products are not generic** medicinal products, since it could be expected that there may be **subtle differences** between similar biological medicinal products from different manufacturers or compared with reference products, which **may not be fully apparent until greater experience in their use has been established**. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified."

Pharmacological classification of biological and biotechnological substances in accordance with WHO

• Drugs for alimentary tract and metabolism: insulins.

•Anti-infectives: antimicrobial, bactericidal permeability increasing polypeptides, human papilomavirus.

•Antineoplastics: peptide vaccines, recombinant vaccines, toxins.

•Blood and agents acting on the heamopoietic system: antithrombins, blood coagulation cascade inhibitors, blood coagulation factors, erythropoietin type blood factors, heparin derivatives including low molecular mass heparins (heparinoids), hirudin derivatives, trombomodulins.

•Immunomodulators and immunostimulants: colony stimulating factors, inteferons, interleukin receptor antagonists, interleukin type substances, monoclonal antibodies , receptor molecules, native or modified, tumor necrosis factor antagonists.

•Hormones, hormone antagonists, hormone-release stimulating peptides or hormone-release inhibiting peptides (excluding insulins): growth hormon (GH) derivatives, its antagonists, oxytocin derivatives, pituitary / placental glycoprotein hormones, pituitary hormone-release stimulating peptides, synthetic polypeptides with cortikotropin-like action, vasoconstriktors, vasopressin derivatives.

•Various: „antisense“ oligonucleotides, enzymes, gene therapy products, growth factors, peptides a glycopeptides not classified above.

Basics of biologics nomenclature in accordance with WHO recommendations

[INTERNATIONAL NONPROPRIETARY NAMES (INN) FOR BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES (A REVIEW) INN Working Document 05.179 Update December 2010]

2.1. Groups with respective stem

Name of the group	Stem
antisense oligonucleotides	*-rsen*
blood coagulation cascade inhibitors	*-cogin*
blood coagulation factors	*-cog*
colony stimulating factors	*-stim*
enzymes	*-ase*
erythropoietin type blood factors	*-poetin*
growth factors	*-ermin*
growth hormone derivatives	*som-*
heparin derivatives including low molecular mass heparins	*-parin*
hirudin derivatives	*-irudin*
pituitary hormone-release inhibiting peptides	*-relix*
interleukin receptor antagonists	*-kinra*
interleukin type substances	*-kin*
monoclonal antibodies	*-mab*
oxytocin derivatives	*-tocin*
peptides and glycopeptides (for special groups of peptides see *-actide*, *-pressin, -relin, -tocin*)	*-tide*
pituitary hormone-release stimulating peptides	*-relin*
receptor molecules, native or modified (a preceding infix should designate the target)	*-cept*
synthetic polypeptides with a corticotropin-like action	*-actide*
vasoconstrictors, vasopressin derivatives	*-pressin*

Basics of biologics nomenclature in accordance with WHO recommendations (continued)

2.2 Groups with respective pre-stems

Name of the group	Pre-stem
antimicrobial, bactericidal permeability increasing polypeptides	*-ganan*

2.3 Groups with INN schemes

Name of the group
antithrombins
gene therapy products
insulins
interferons
pituitary / placental glycoprotein hormones

Basics of biologics nomenclature in accordance with WHO recommendations (continued)

2.4 Groups without respective stems / pre-stems and without INN schemes

Name of the group
growth hormone antagonists
human papilloma virus
peptide vaccines / recombinant vaccines
thrombomodulins
toxins

3.6. General policies for monoclonal antibodies [1] [3] [11]3

- INN for monoclonal antibodies (mAbs) are composed of a prefix, a substem A, a substem B and a suffix.
- The common stem for mAbs is -*mab,* placed as a suffix.
- The stem -*mab* is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.
- Substem B indicates the species on which the immunoglobulin sequence of the mAb is based (shown in Table 2).

Table 2 Substem B for the species

a	rat
axo (pre-sub-stem)	rat/mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
-xizu- (under discussion)	chimeric-humanized
zu	humanized

Chimeric vs. humanized monoclonal antibodies

The distinction between chimeric and humanized antibodies is as follows:

A chimeric antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable domain of both heavy and light chains linked to heavy and light constant regions of human origin.

A humanized antibody has segments of foreign-derived amino acids interspersed among variable domain segments of human-derived amino acid residues and the humanized variable heavy and variable light domains are linked to heavy and light constant regions of human origin.

The *–xizu-* infix is used for an antibody having both chimeric and humanized chains.
The *-axo-* infix is used for an antibody having both rat and mouse chains.

Nomenclature of monoclonal antibodies – continued

•a **sub-stem A for** disease or target class is situated before a sub-stem for source of the product

Table 3 Substem A for target class

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

In principle, a single letter, e.g. *-b-* for bacterial is used as substem A. Whenever substem B starts with a consonant (e.g. x or z), to avoid problems in pronunciation, an additional vowel indicated in the table, e.g. *-ba-* is inserted.

Nomenclature of monoclonal antibodies – continued

Special sub-stems for tumours were in the older version of INN rules from 2007 and are not recommended in the newer one

tumours:

-co(l)-	colon
-go(t)-	testis
-go(v)-	ovary
-ma(r)-	mammary
-me(l)-	melanoma
-pr(o)-	prostate
-tu(m)-	miscellaneous

Whenever there is a problem in pronunciation, the final letter of the sub-stems for diseases or targets may be deleted, e.g. *-vi(r)-*, *-ba(c)-*, *-li(m)-*, *-co(l)-*, etc.

Nomenclature of monoclonal antibodies – continued

Prefix

Should be random e.g. the only requirement is to contribute to a euphonious and distinctive name.

An example of the INN name of a monoclonal antibody

humanized
↓
prefix→**bevacizumab**
↑
cardiovascular

Disadvantages of biologics (except adverse effects, which are in general the same as in small molecules)

- **imunogenicity** – induction of formation of antibodies against the drug
- HAMA – human anti-mouse antibodies – formed against mouse peptide sequences in chimeric biologics (similarly HARA – human anti-rat antibodies)
- greater than 20% of murine antibodies induce only tolerable/negligible immunogenicity
- HAHA – human anti-human antibodies – formed against fully human antibodies or other biologics; bound to a unique binding site, where they are not tolerated by the immunity system
- humanization of some murine antibodies may reduce their clinical effectiveness
- neutralizing × non-neutralizing; if they are neutralizing, they attenuate the efficacy of treatment
- formation of antibodies against drugs (e.g. compounds acting against TNF) depends also on presence of infection
- **high price**
- **activity and security frequently insufficiently guaranteed**
- **poor biological availability requiring special methods of application**