

K+F ÉS LABORATÓRIUMI MENEDZSMENT KURZUS

Biotechnológus MSc képzés

**Budapesti Műszaki és Gazdaságtudományi
Egyetem**

Benkő Zsuzsa, Kollár Éva, Sütő Zoltán

Process design and process development

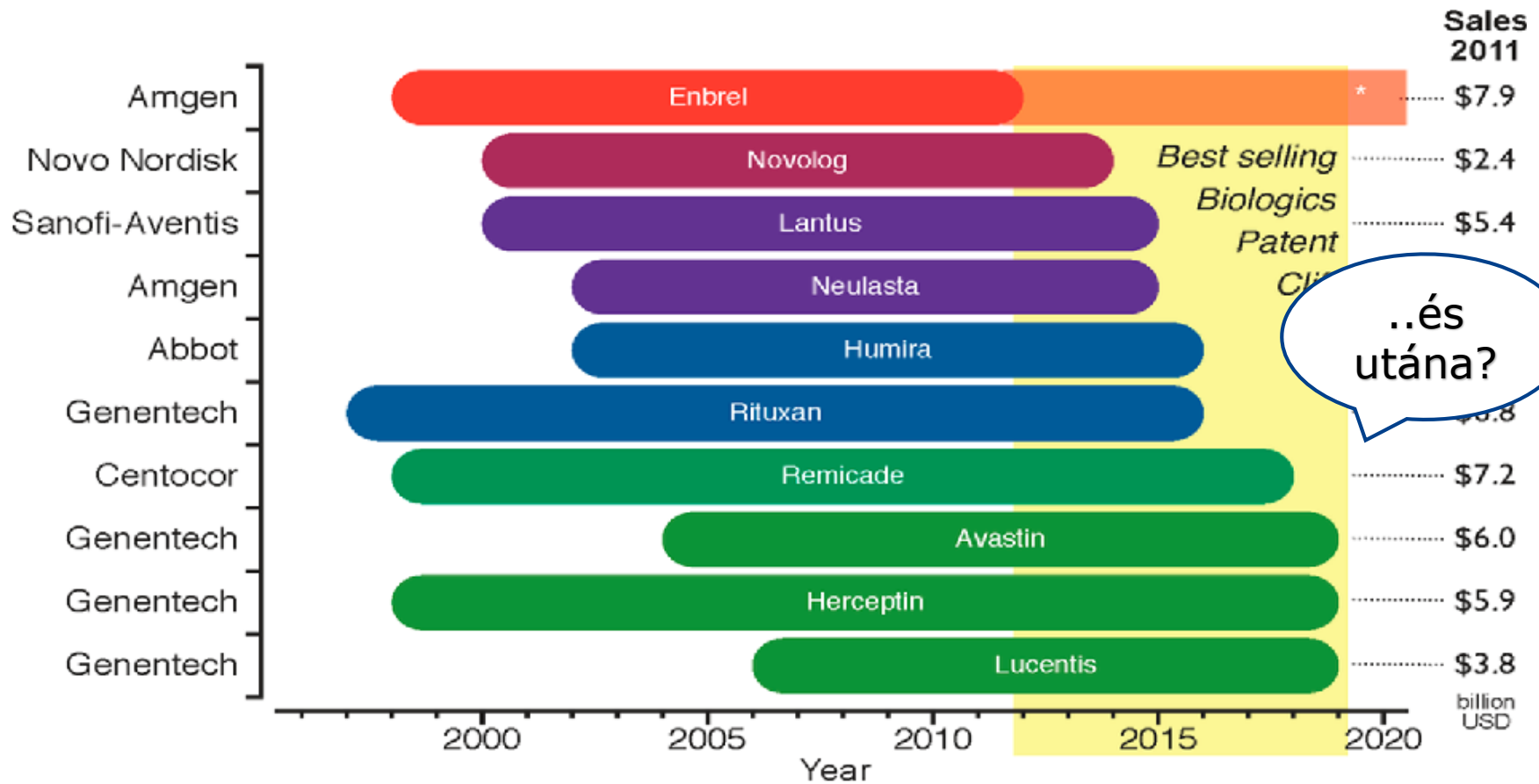
Sütő Zoltán



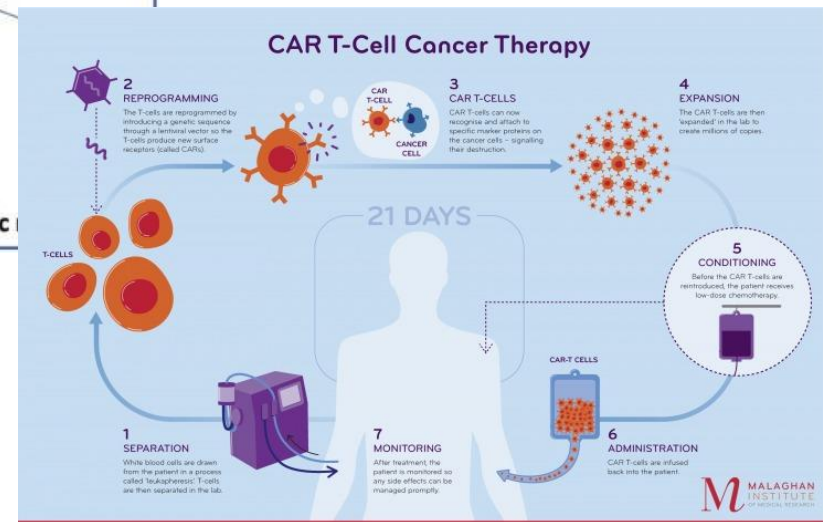
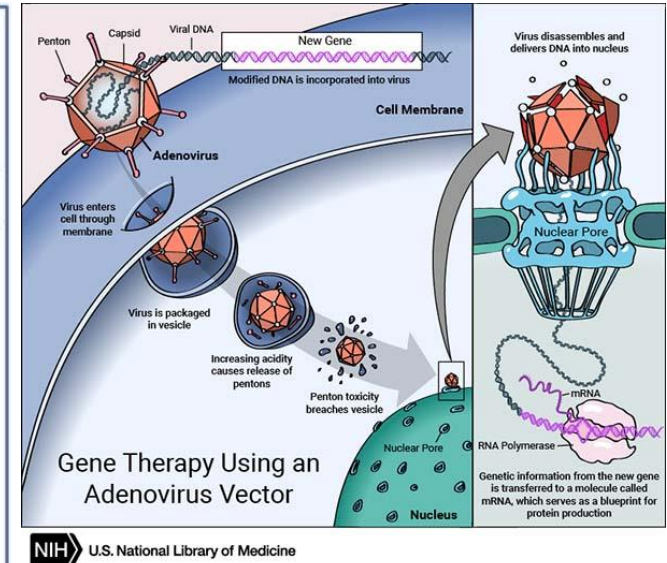
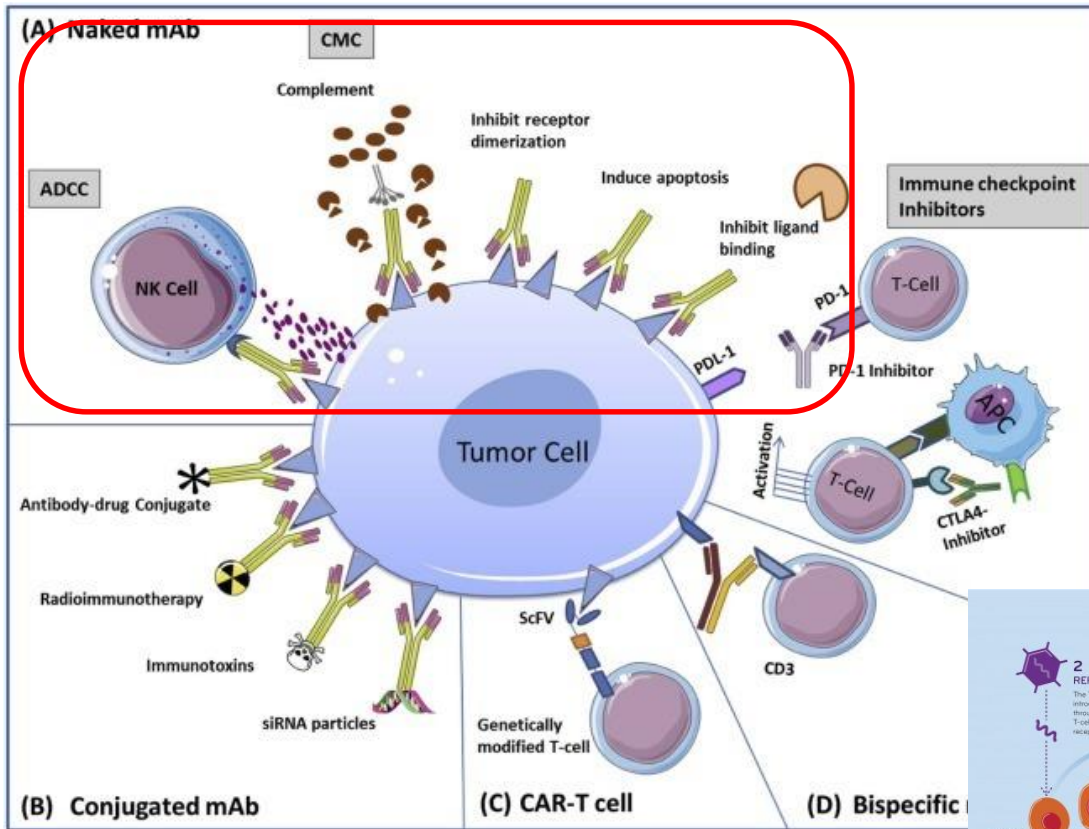
Bioszimiláris piac



Bioszimiláris „Golden cliff”



Terápiás utak



Üzletfejlesztési megfontolások - stratégia

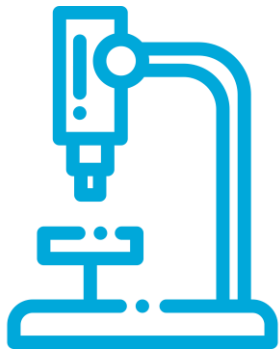
- **Indikációs/terápiás terület (onkológia, autoimmun, ritka megbetegedések)**
- **Piaci szegmens (harmonizált vagy egyedileg regulált piacok)**
- **Blockbuster vs niche termékek (orphan drug/ritka megbetegedések)**
- **Vállalati termékportfólió**
- **Vállalati adottságok – fejlesztési, termelési képesség és know-how**
- **Partneri kapcsolatot és képesség – rizikó és költség diverzifikáció**
- **Termék várható életciklusa - megtérülési ráta, fenntarthatóság (alternatív termékek), termék veszélyessége (containment)**
- **Versenykörnyezet – várható piaci részesedés**

Biotechnology is one of the three specialty pharma departments at Gedeon Richter



Specialty Pharma

Original research



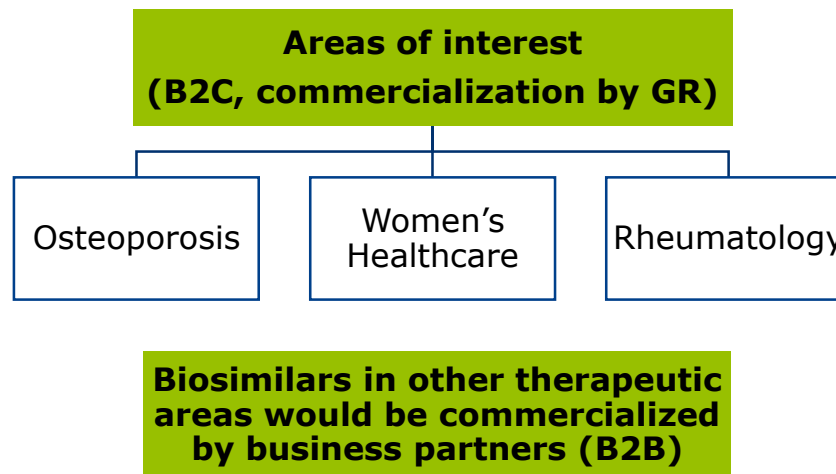
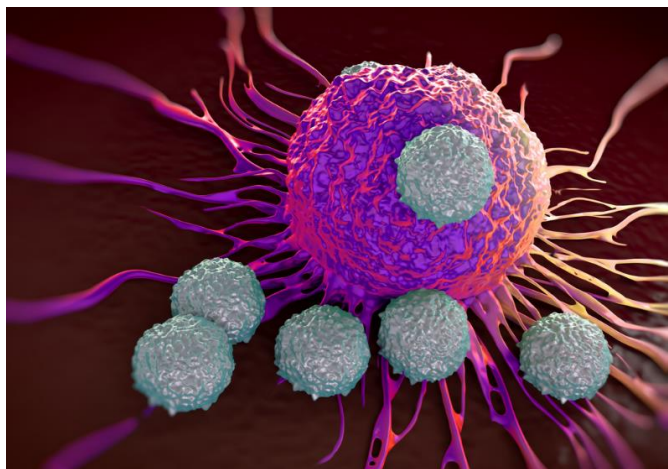
Biotechnology



**Women's
healthcare**



Portfolio of the Biotechnology Business Unit



Product	Indication	Status
BEMFOLA® (biosimilar r-hFSH)	Infertility	Richter acquired the product in 2016, marketed in more than 30 countries
TERROSA® (biosimilar teriparatide)	Osteoporosis	EU marketing authorization received in January 2017, launch in August 2019
Pegfilgrastim	Neutropenia	Late stage clinical development

Additional 2 undisclosed biosimilars in early stage development

A példa: a bevacizumab hatóanyag

Identification

Name	Bevacizumab
Accession Number	DB00112 (BTD00087, BIOD00087)
Type	Biotech
Groups	Approved, Investigational
Description	A recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons.

Protein chemical formula $C_{6538}H_{10034}N_{1716}O_{2033}S_{44}$

Protein average weight 149000.0 Da

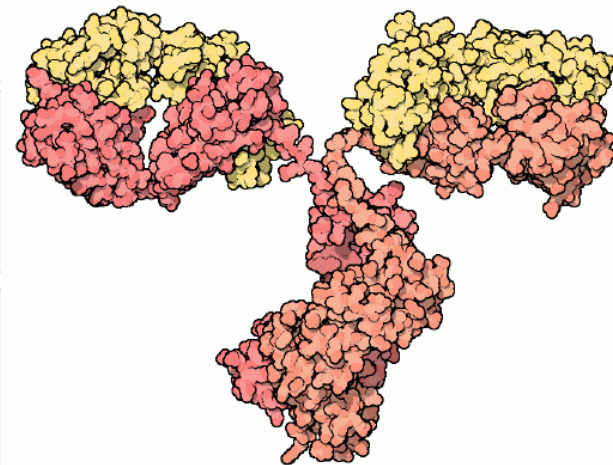
Sequences

>"Bevacizumab light chain"

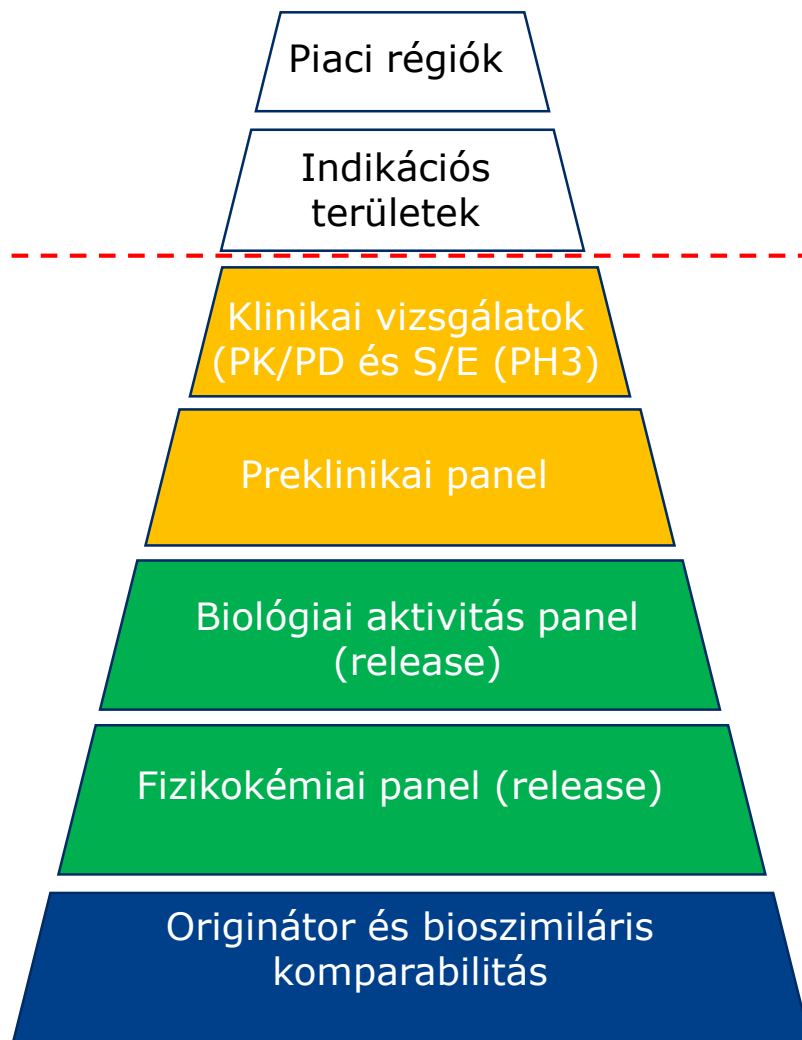
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DIQMTQSPSSLSASVGRVTITCSASQDISNYLNIWYQQKPKGKAPKVLIIYFTSSLHSGVPS  
RFSGSGSGTDFTLTISLQPEDFATYYCQYSTVPWTFGGTKVEIKRTVAAPSVEIFPP  
SDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSLSTLT  
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

>"Bevacizumab heavy chain"

```
EVQLVESGGGLVQPGGSLRLSCAASGYFTNYGMNWRQAPGKGLEWVGWINTYTGPTY  
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYGSSHWYFDVWGQGLVLT  
VSSASTKGPSVFLPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVL  
QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPEL  
LGGPSVFLFPPPKPDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPREE  
QYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS  
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDK  
SRWQQGNVFSQSVMHHEALHNHYTQKLSLSLSPGK
```



Minőségi szintek



Piaci környezet

Vállalati környezet

Hatóanyag/Termék minőségi profil – QTPP, a céltábla

Minőségi jellemzők:
cQA1
cQA2
...

Critical Quality Attribute	Product	Comparability range	Bar Graph
G0F %			
G1F %			
G1'F %			
G2F %			
Total AF %			
Total HM %			
NANA µg/mg			
NGNA µg/mg			
Binding VEGF-A %			
VEGF signalling reporter assay %			
Total acidic variants % (Intact)			
K0+K1 % (Intact)			
Other basic variants % (Intact)			
Aggregates %			
Monomer %			
Fragments %			

Number of RMP batches n = 19
 ***n = 5
 ****n = 8
 *****n = 9
 *****n = 15

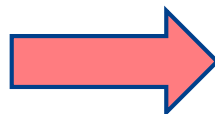
Number of RGB-09 DS batches (100L) n = 3
 *n = 2

tartomány

QTPP: quality target profile
 cQA: critical quality attribute
 CPP: critical process parameter

Technológia (fejlesztés) elemei

Sejtvonal fejlesztés



**Hatóanyag
fejlesztés**



Készítményfejlesztés

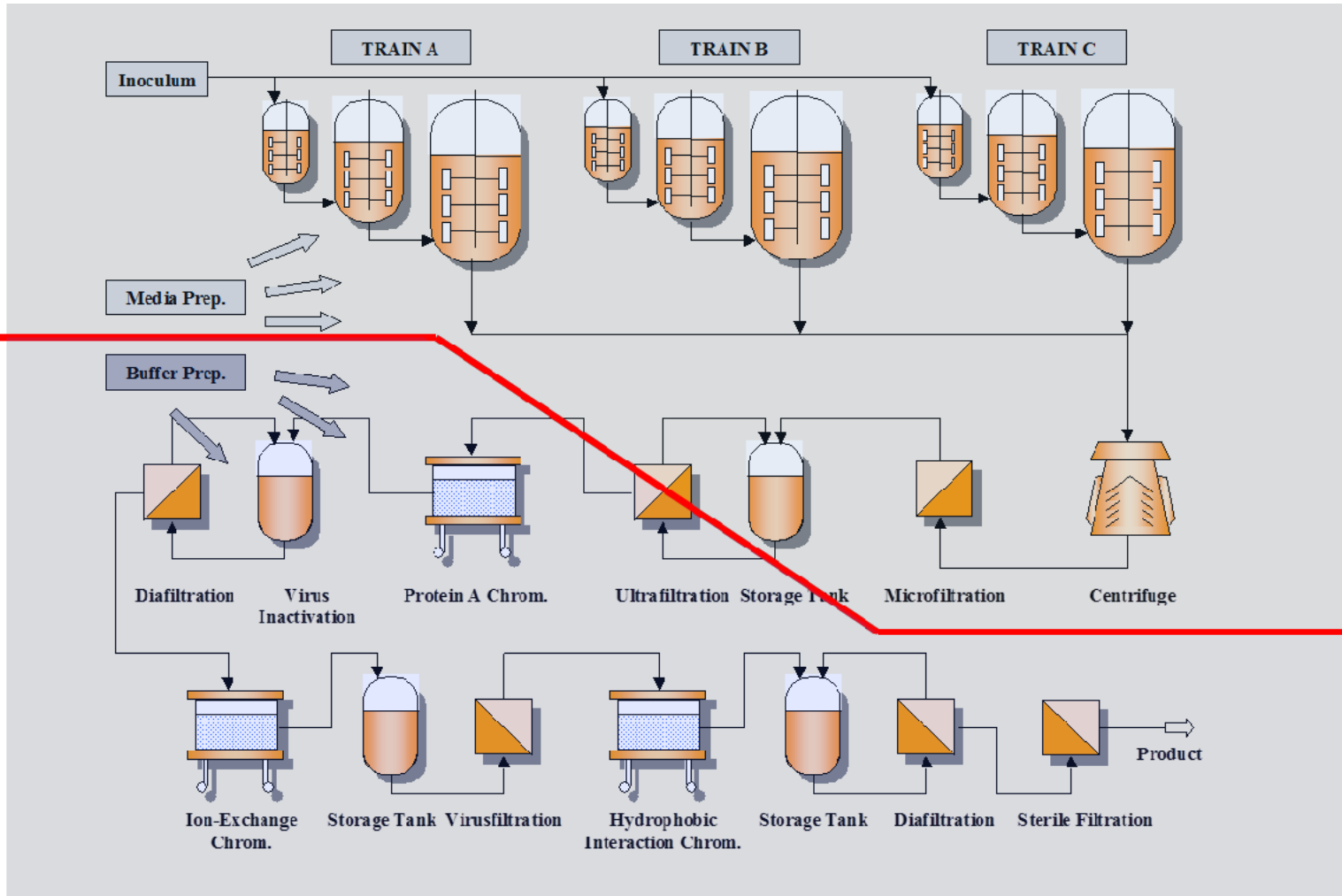


Analitika

Hatóanyag technológia

USP

DSP



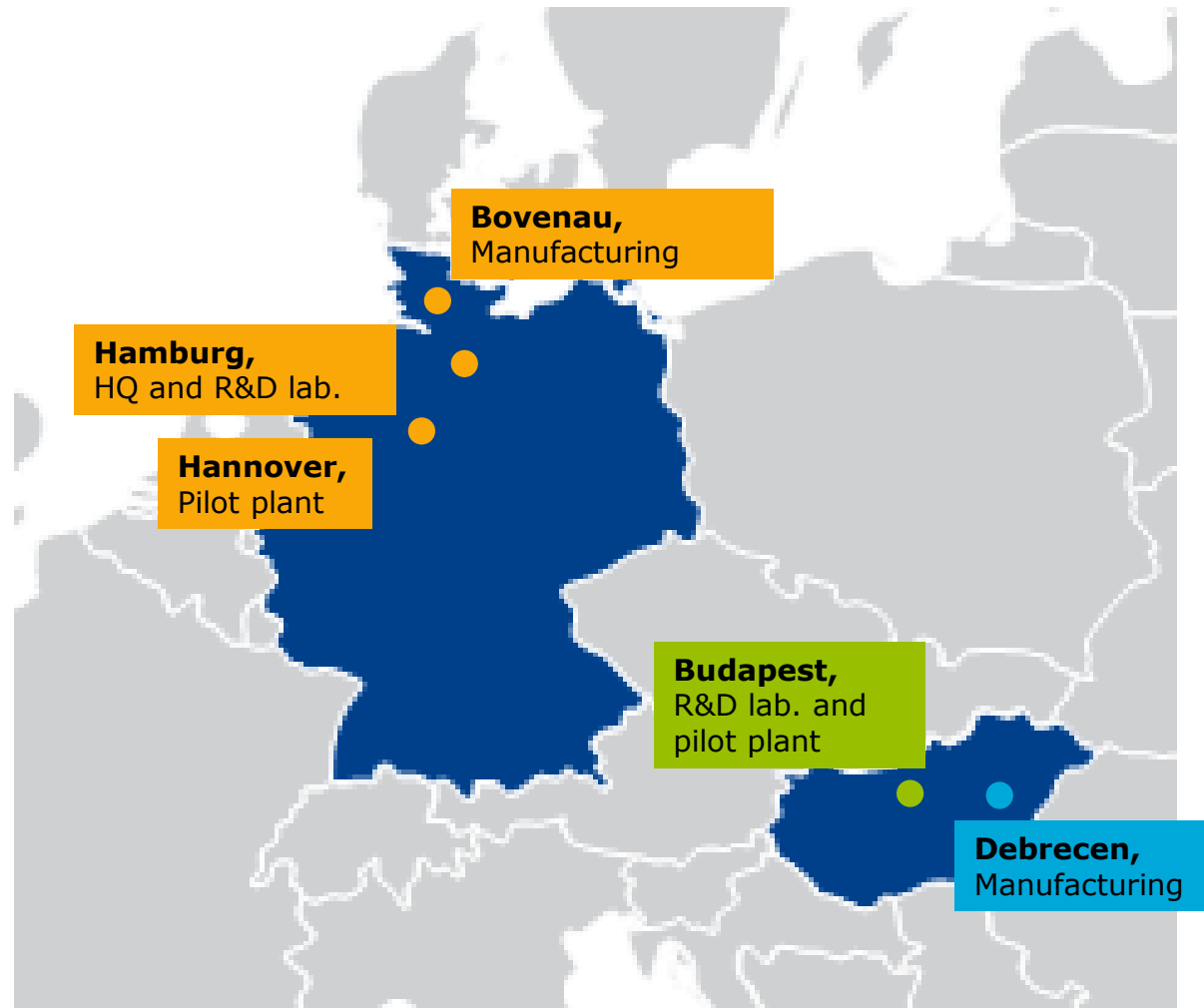
Schematic manufacturing process of monoclonal antibodies from cell culture, <https://www.semanticscholar.org/paper/Trends-in-Upstream-and-Downstream-Process-for-Gronemeyer-Ditz/e6aa263f5f0b04c1efbbe087798af1db23219a58/figure/1>

Biotechnology facilities – gazda platform

2007: Richter-Helm
Biologics - joint venture
with Helm AG

2007: Establishing first
laboratories in Budapest

2012: Debrecen biotech
plant put into operation



Upstream fejlesztés – sejtvonal kiálasztás



Rekombináns sejtvonal
Chinese **H**amster **O**vary (CHO)



Rázólombikos tenyésztés
(inokulum)



Bioreaktoros tenyésztés
(fehérjetermelés)



© Reactors
<http://www.stabletransfection.com/transient-transfection/>



<https://www.presens.de/knowledge/publications/application-note/accurate-insight-into-oxygen-content-of-shake-cultures-582.html>



<https://www.sartorius.de/sartoriusDE/de/EUR/products/bioreactors-fermentors/single-use/ambr-15-cell-culture>

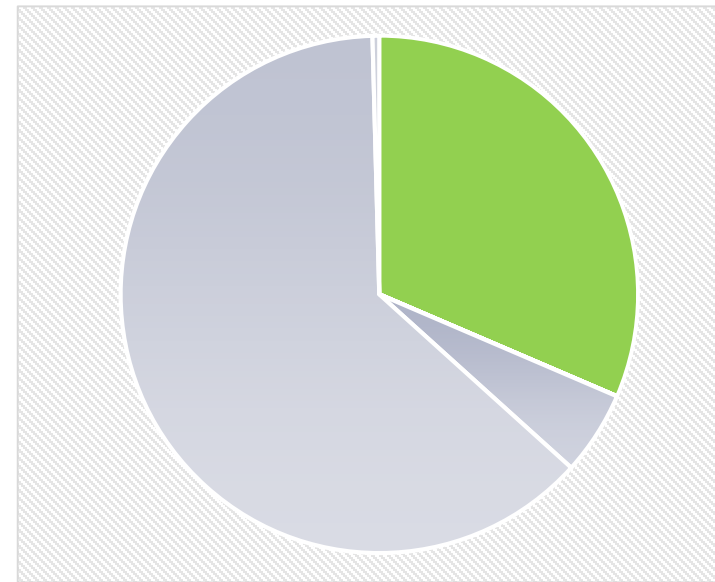
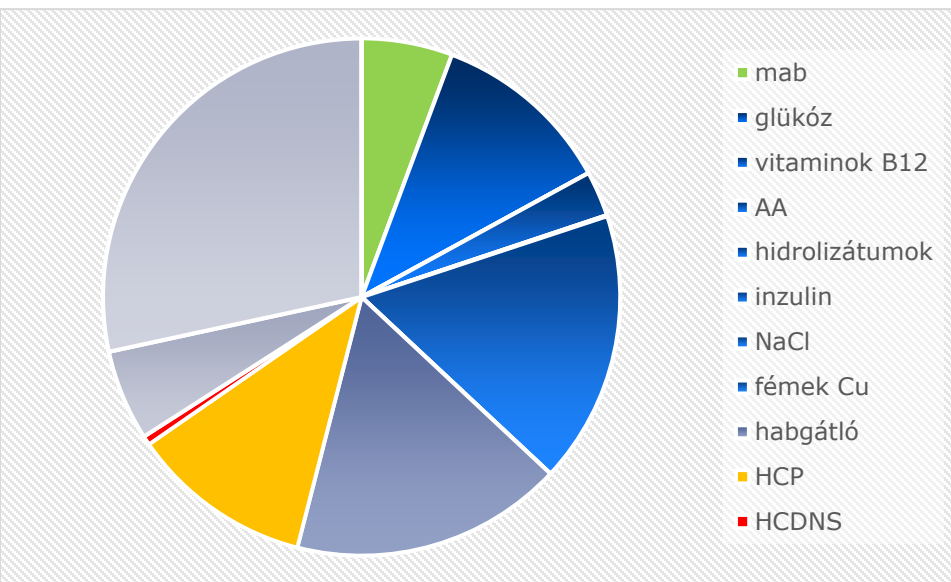


http://fenix-sd.com/content/user_files/File/Biostat_B_plus.pdf



<https://www.selectscience.net/products/biostat-cultibag-str-plus/?prodID=93490>

A nyers harvest VS a hatóanyag oldat szárazanyag-összetétele

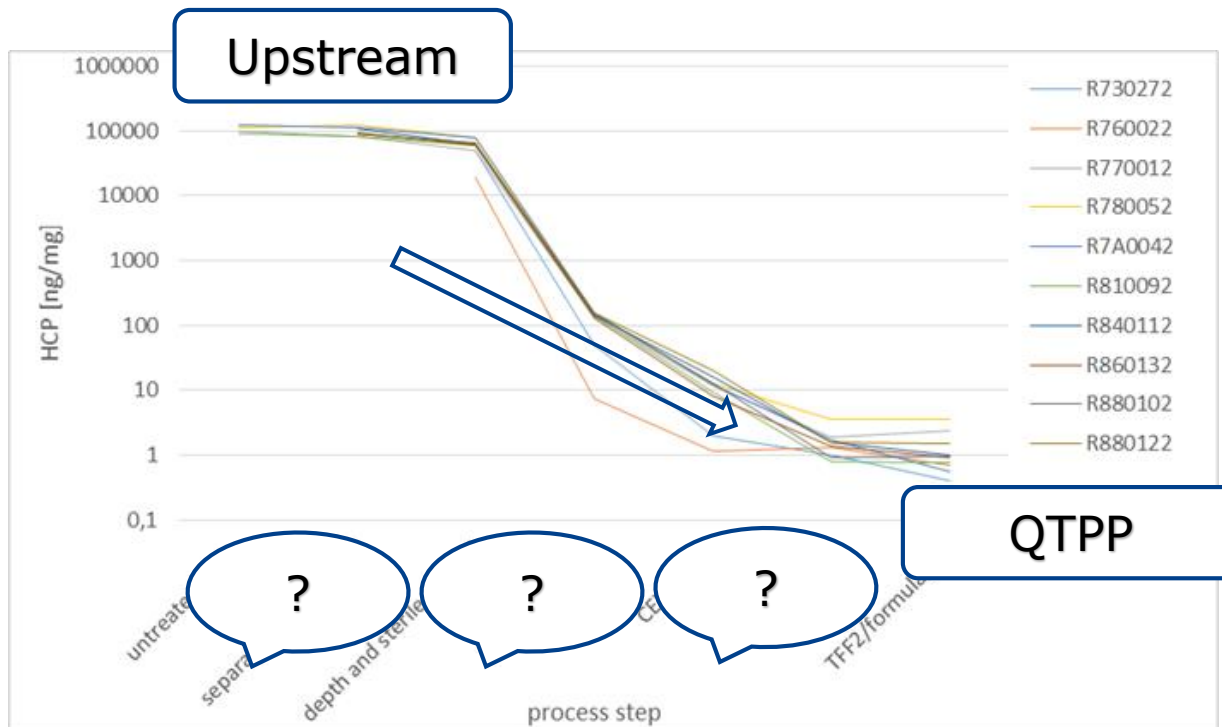


A downstream definíciója

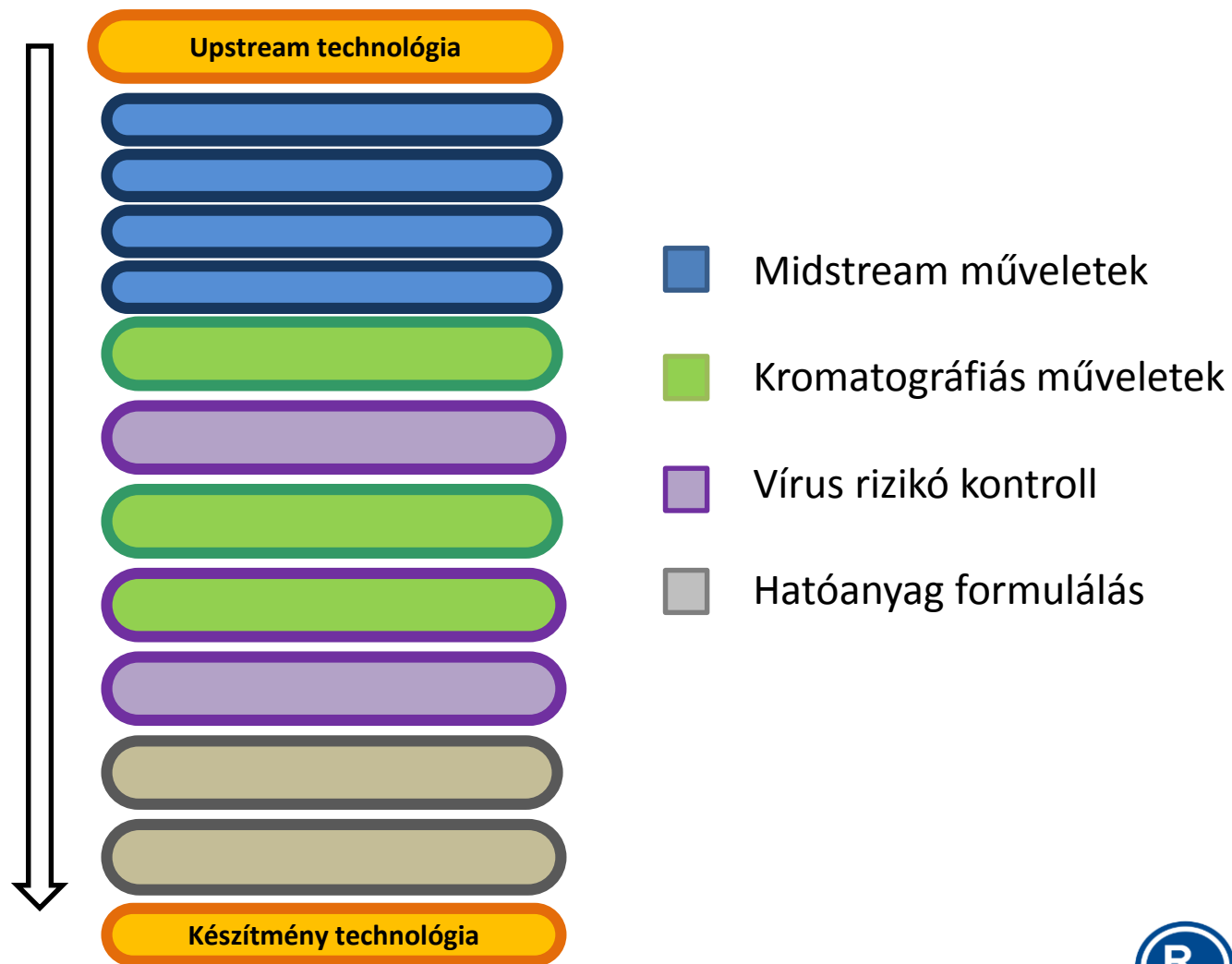
- **Downstream processing** refers to the recovery and purification of biosynthetic products, particularly pharmaceuticals, from natural sources such as animal or plant tissue or fermentation broth.
- Downstream processing and analytical bioseparation both refer to the separation or purification of biological products, but at **different scales** of operation and for **different purposes**.
- Downstream processing implies manufacture of a purified product fit for a specific use, generally in marketable quantities, while analytical bioseparation refers to purification for the sole purpose of measuring a component or components of a mixture, and may deal with sample sizes as small as a single cell.


A nyers harvest VS a hatóanyag oldat összetétele

II. – cQA1



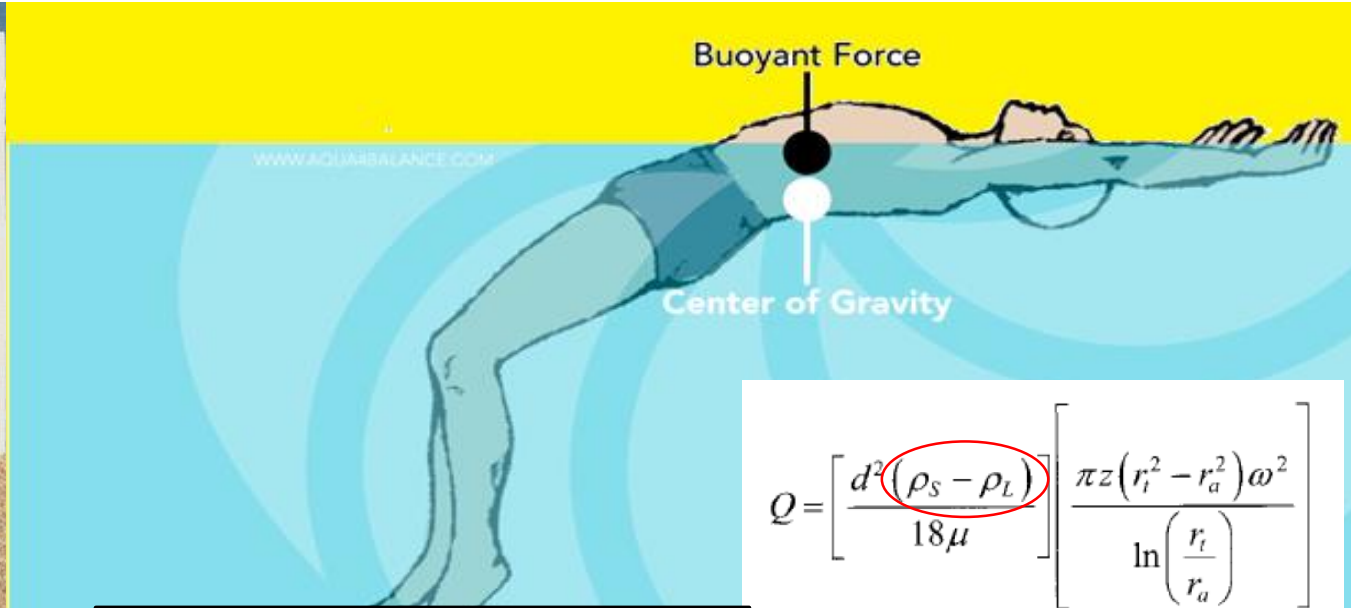
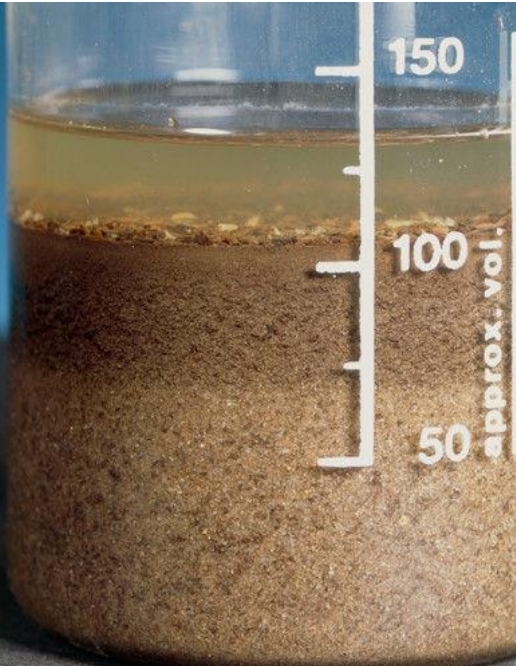
Célunk: feldolgozási sor kialakítása





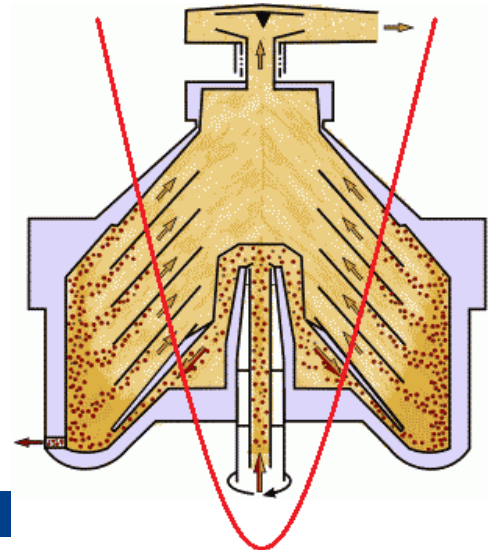
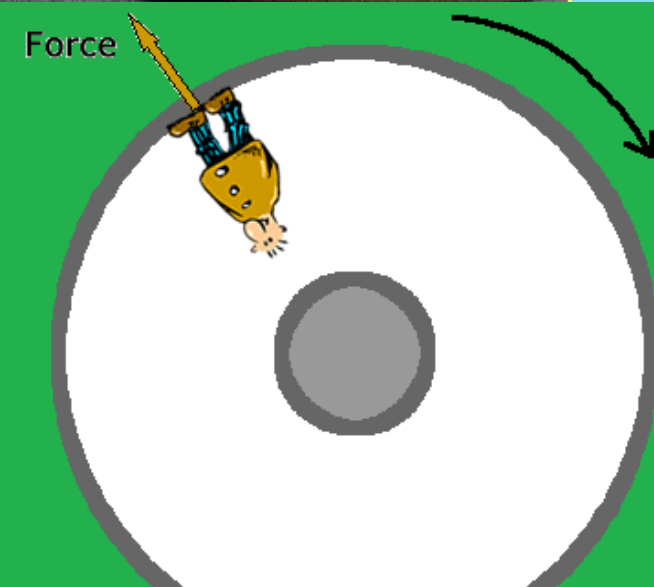
■ Midstream műveletek

Szeperálás: sűrűségkülönbség

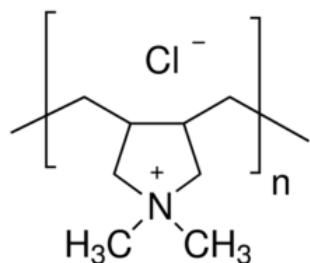


$$Q = \left[\frac{d^3(\rho_s - \rho_L)}{18\mu} \right] \left[\frac{\pi z (r_i^2 - r_a^2) \omega^2}{\ln\left(\frac{r_i}{r_a}\right)} \right]$$

- sejt, sejtörmelék eltávolítás
- oldhatatlan csapadék eltávolítás

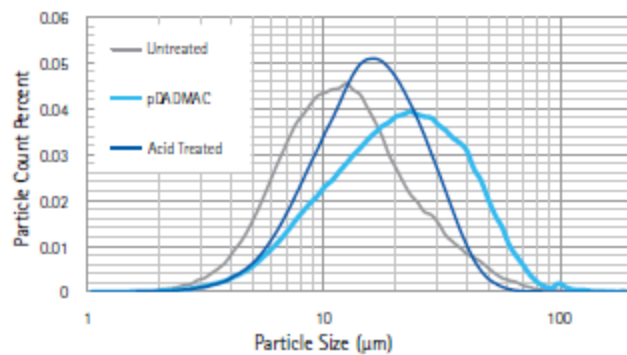


Csapadékképzés: oldhatóság

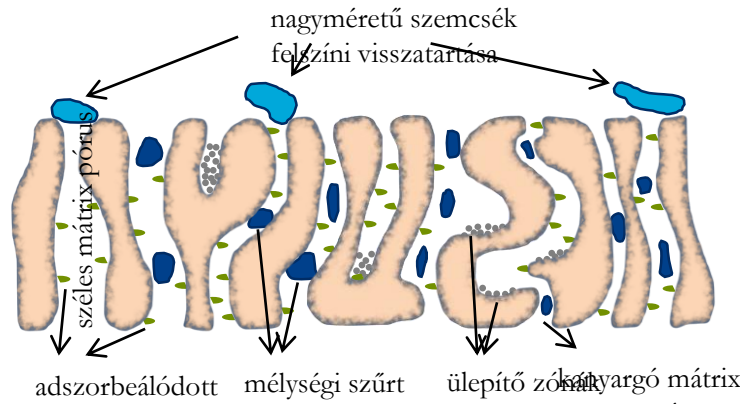
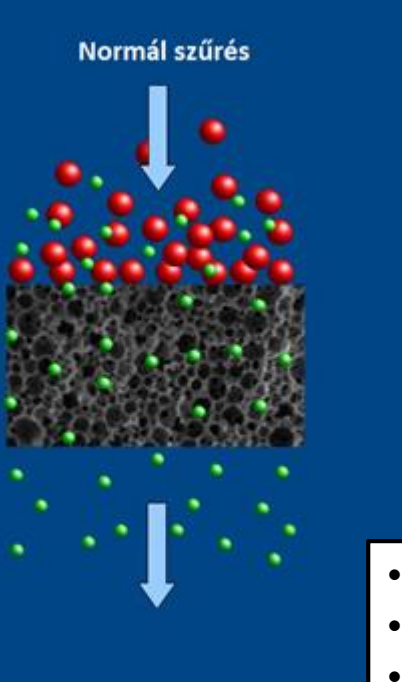


- Termék vagy HCP&HCDNS oldhatóság csökkentése
- csapadékképzés

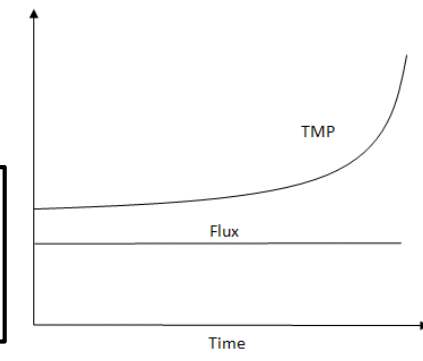
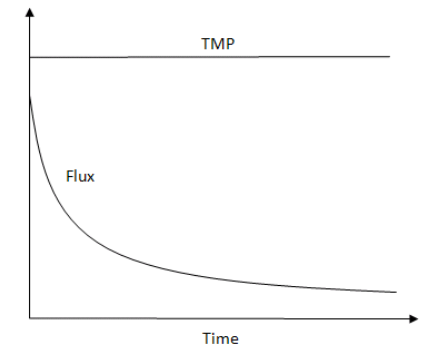
Figure 2. Partical size distribution



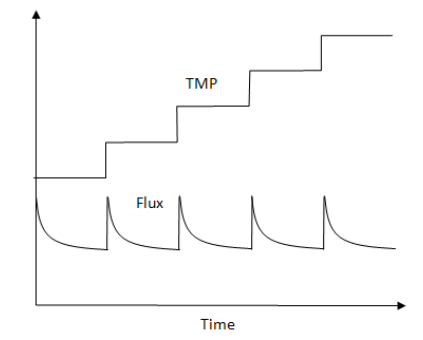
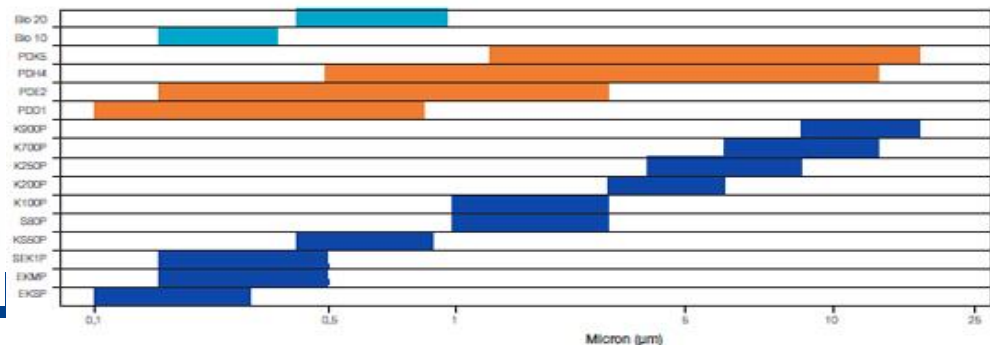
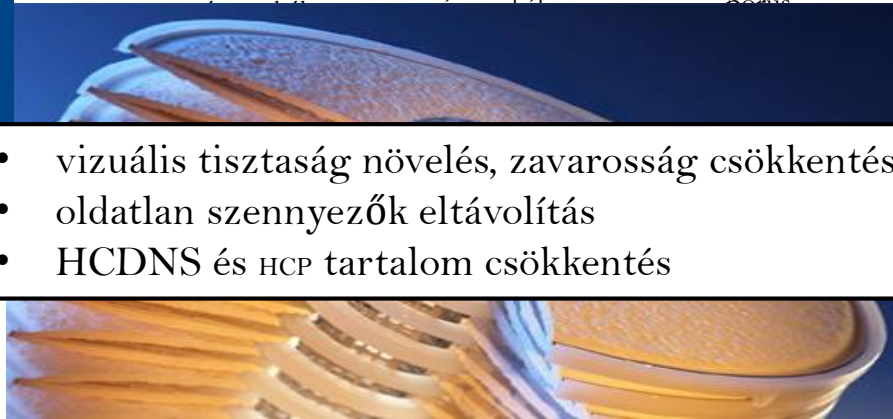
Mélyésgyi szűrés: méretkülönbség és ...



áramlás iránya



- vizuális tisztaság növelés, zavarosság csökkentés
- oldatlan szennyezők eltávolítás
- HCDNS és HCP tartalom csökkentés





 Kromatográfiás műveletek

Kromatográfia: töltéssűrűség, specifitás...

tag, specifikus régiók megléte:

- Fc, Fab: protein A, protein G, protein L
- His-tag: IMAC, TALON

Izoelektromos pont, pI:

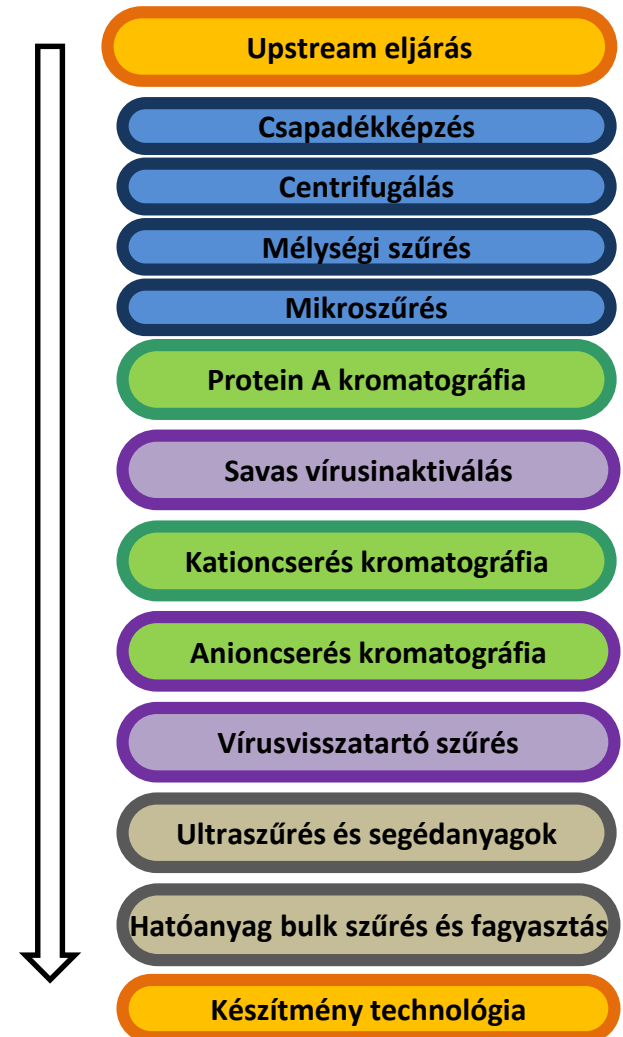
- IEX: (ion exchange)
- AEX: (anion exchange)
- CEX: (cation exchange)

Hidrofób-patch-ek:

- HIC: (hydrophobic interaction chromatography)
- RPC: (revers phase chromatography)

Hidrodinamikai sugár:

- SEC: (size exclusion)

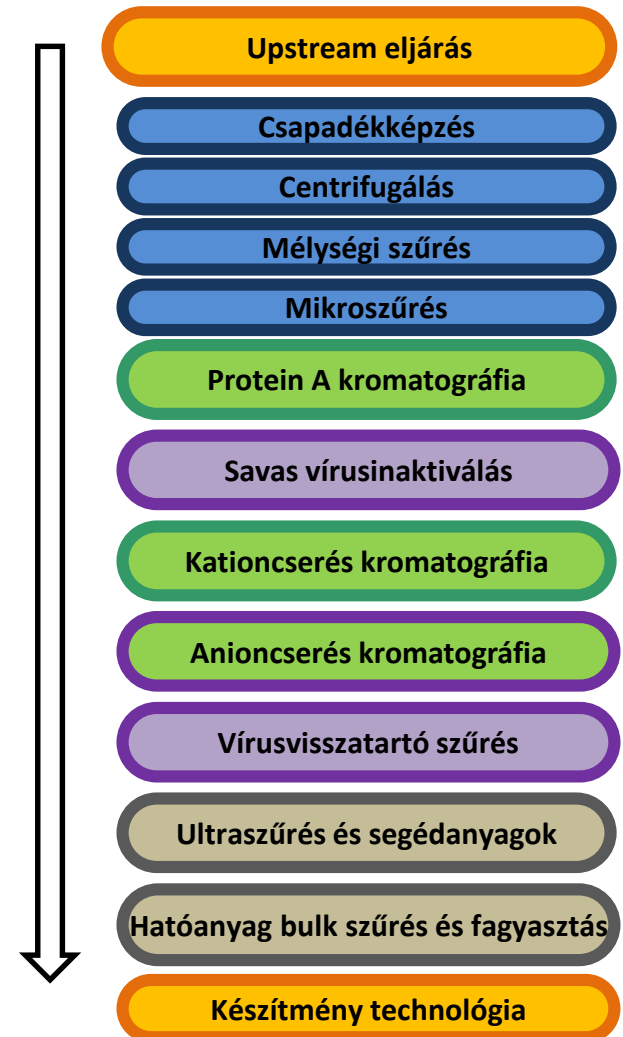




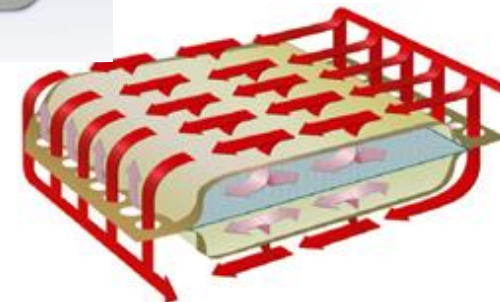
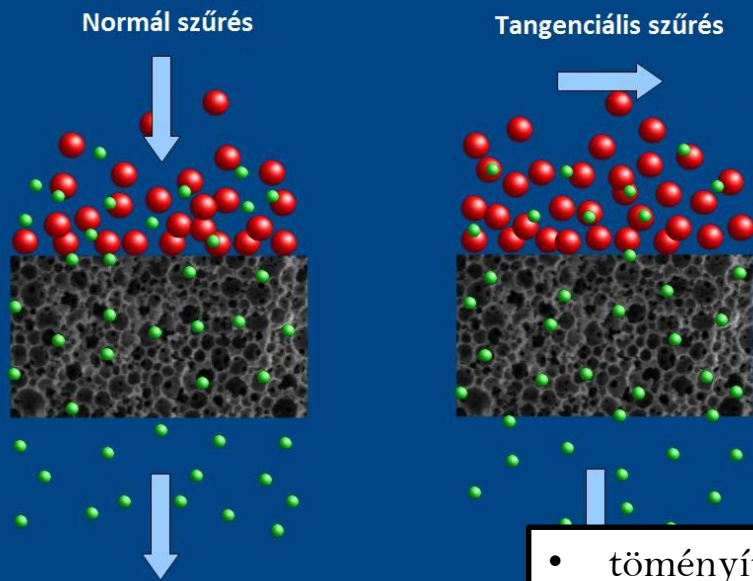
Hatóanyag formulálás

Formulálás: molekulaméret szerinti szeparáció

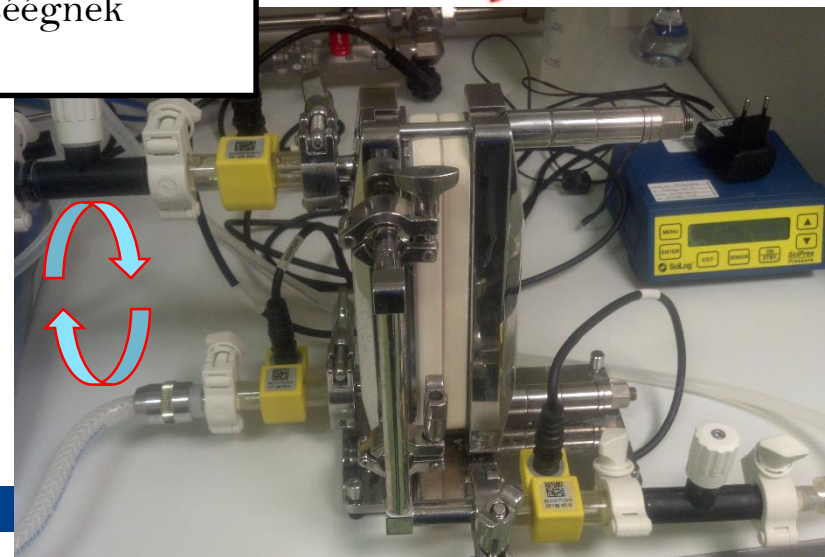
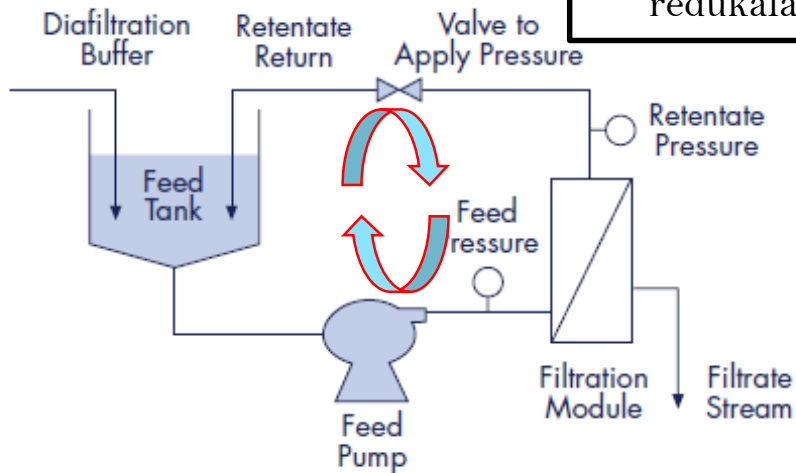
- **Molekuláris környezet cseréje, (puffercsere és töményítés)**
- **Vegyipari technikák destruktívak a termékre**
- **Térfogat által befolyásolt:
Segédanyagok hozzáadása
Hőcsere és pH beállítás
Tárolás és anyagszállítás**
- **Mikrobiális rizikó kontroll**



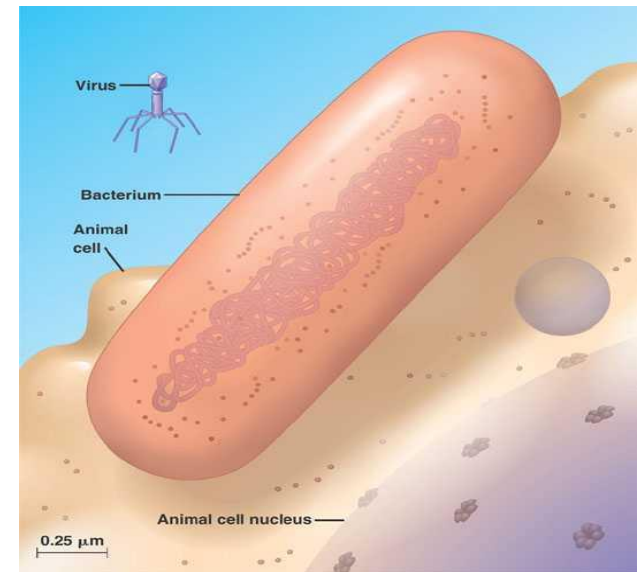
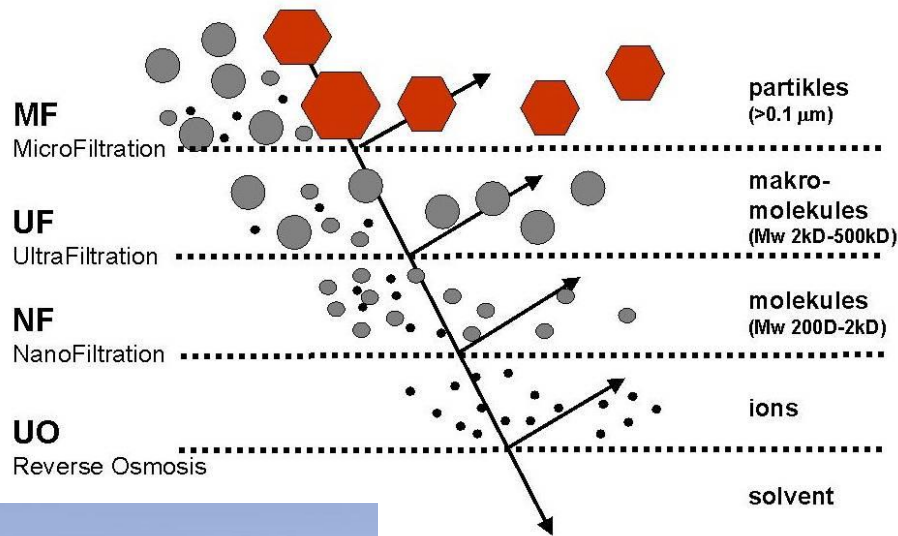
Ultraszűrés: molekulaméret és szolvatáció



- töményítés
- puffercsere
- szennyezők mennyiségének redukálása

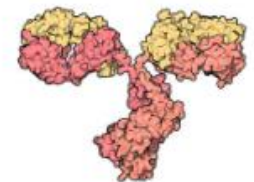
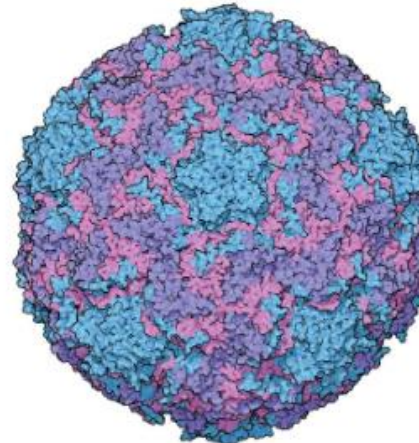


Hatóanyag oldat szűrés: méret szerinti visszatartás

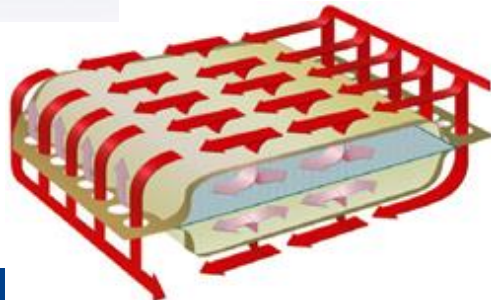


Ultraszűrés (UF)

Nanoszűrés (NF)



P !!!



Process characterization

Control strategy

Benkő Zsuzsa



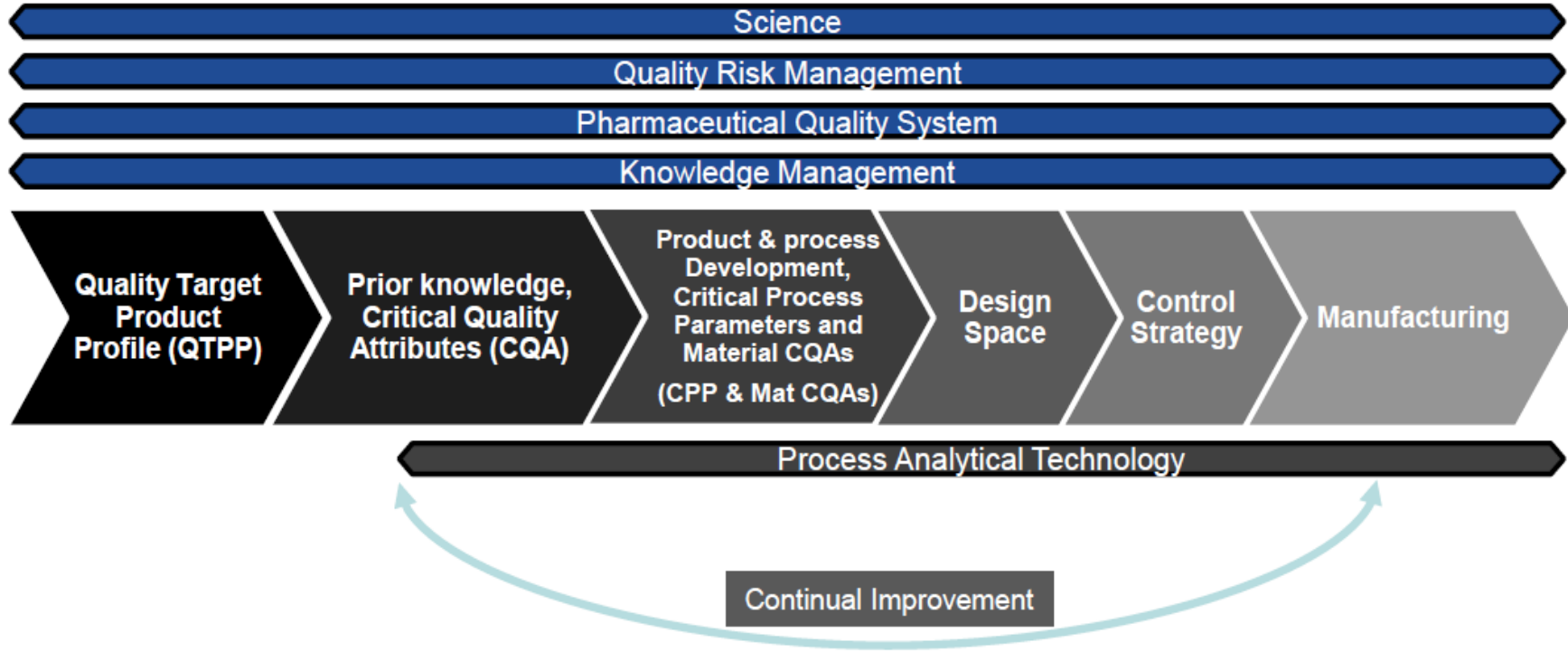
The Quality by Design concepts



Moheb M. Nasr, CDER/FDA, 2010



The QbD Roadmap



QbD - Melyik *guidelineok szabályozzák?*

ICH Q8

- Describes risk-based approach for development of the manufacturing process (DP)
- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQAs)
- Design Space

FOCUS ON P2 of the CTD

ICH Q11

- Development of the manufacturing process
- Selection and justification of the starting material
- Control strategy
- Process validation
- Submission of information in the CTD

FOCUS ON S25 and S26 of the CTD

ICH Q9

Quality risk management

ICH Q10

Quality system

ICH Q8/Q11 training Horn et al 2017



What is the difference between traditional and enhanced Approach?



Aspects	Traditional Approach	QbD
Pharmaceutical Development	Empirical, optimization (sometimes trial and error)	Systematic approach, Multivariate experiments, Focus on process understanding, risk assessment, adequate control strategy, evaluate impact of material attributes and process parameters on CQAs
Manufacturing Process	Fixed	Flexible within given design space , done within the quality system of the company
Process Validation	Traditional	Continuous process verification
Process Control	IPCs	Use of PAT , tracking of process operations/trend analysis
Product Specification	based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	Batch testing	Risk-based control strategy, Use of RTR
Changes	Variations	More regulatory flexibility

QbD - Előnyök/hátrányok, mire figyeljünk?

What might be your Benefit?

- Better process understanding
- Improved control strategy
- Less batch failures
- More flexibility and more efficient change control
- Less post-approval changes
- Cost savings

\$\$\$???? ?



What is important for you? -1-

- Start discussions early within your CMC-Team
- Define benefits and risks of the QbD-strategy
- Check whether the QbD-approach is feasible for you
- Prepare project plans including all necessary activities from development to commercial manufacture
 - Manufacture of developmental batches
 - Manufacture of Pilot/production batches
 - Validation activities
- Define if you want to have meetings with Authorities

What might be your Concerns? -1-

- More front-loading
- More testing
- Additional workload for meetings
- Potential inspections
- More questions during the review process
- Undefined outcome
- Longer time till product is approved



What is important for you? -2-

- Define which information will be available by when internally
- Decide which data should be included in which part of the dossier
 - S.2.5
 - S.2.6
 - P.2
 - P.3
 - R
- Start early with the preparation of the CMC-Dossier
- Plan for the unexpected (**Plan B**)

ICH Q8/Q11 training Horn et al 2017

QbD for Drug Substance/Drug Products

Quality Target Product Profile (QTPP):

- A prospective **summary of the quality characteristics of a drug product** that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product

CQA (Critical Quality Attribute)

- Physical, biological or microbiological property or characteristic **that should be within an appropriate limit, range or distribution** to ensure the desired product quality
- For drug substance, excipients, intermediates and drug product

Critical Process Parameter (CPP):

- A process parameter whose variability has an impact on a **critical quality attribute** and therefore should be monitored or controlled to ensure the process produces the desired quality.

már a fejlesztés legelején
legyen céltábla

Design Space

- The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
- **Working within the design space is not considered as a change**
- Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process
- **Design space is proposed by the applicant and is subject to regulatory assessment and approval.**

Proven acceptable range (PAR)

- A characterized **range of a process parameter** for which operation **within this range**, while keeping other parameters constant, will result in producing a material **meeting relevant quality criteria.**

Mit tekintünk kritikusnak?

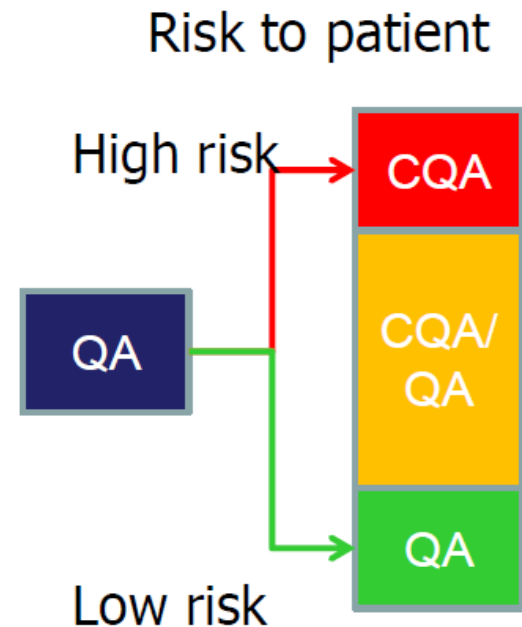
ICH Q8/Q11 training Horn et al 2017



Kritikusság – kontinuum 1.

When is a Quality Attribute a CQA?

- ❑ When the quality attribute has an impact on the patient, examples
 - Efficacy: “what if the patient get the wrong dose”
 - Safety: What if the product has degradants
 - Quality: What if the product is damaged – will the patient take it?
- ❑ Continuum of criticality – cascade from “critical” to “not critical”



ICH Q8/Q11 training Horn et al 2017

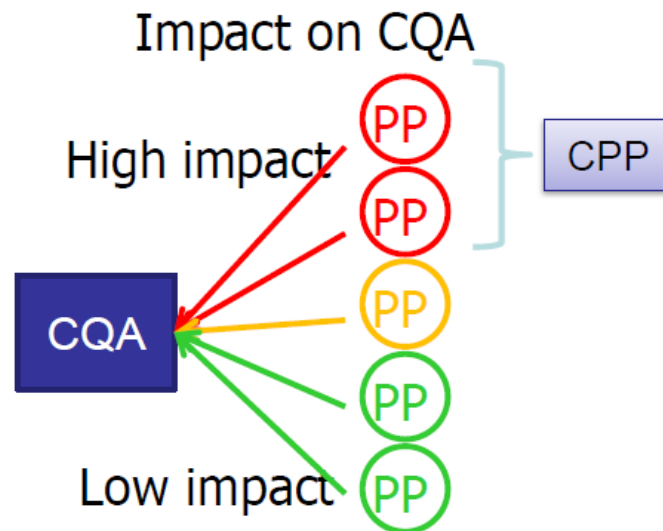


Kritikusság – kontinuum 2.

When is a process parameter a CPP?

- ❑ A process parameter is a Critical Process Parameter when it has a high impact on a CQA
- ❑ A CPP contribute to ensuring the CQA meets the acceptance criteria
- ❑ The CPPs are identified from a list of potential CPPs, a risk assessment and experimental work on these potential CPPs

Probability to impact the CQA and ability to detect the impact drives the criticality decision



Ⓟ is a process parameter

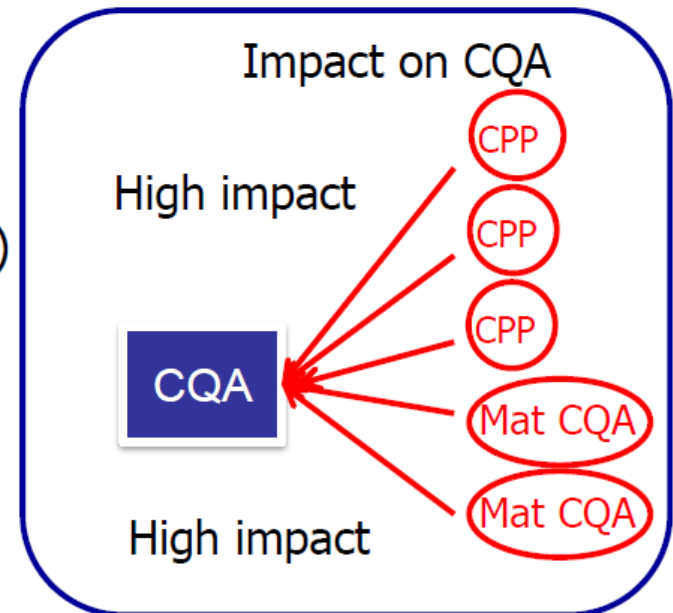
Technológia fejlesztés feladata

Connection between CQA, Material CQAs and CPPs



- ❑ A drug substance CQA, e.g. particle size distribution can be a material CQA for the drug product CQA
- ❑ A CQA is dependant on both material critical quality attributes and critical process parameters

$$\text{CQA} = f(\text{mat CQA}_1, \text{mat CQA}_i, \text{CPP}_1, \text{CPP}_2, \text{CPP}_j)$$



Eljárás karakterizálás - definíció

Process evaluation

Studies, performed at small and/or commercial scale, should **provide evidence** that the complete manufacturing process and each step/operating unit have been appropriately designed and are controlled to obtain a product of the intended quality.

Process validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Product Lifecycle stages (ICH Q10)

Pharmaceutical
Development

Technology
Transfer

Commercial
Manufacturing

Product
Discontinuation

Eljárás karakterizálása – mit jelent?

Process characterization is an essential step in the commercialization of a new (biological-) drug. For drug product commercialization, manufacturers must validate the drug's manufacturing process. This ensures, that the manufacturing process delivers consistently a quality product and that the patient is not at risk.

Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

Recently, US and European regulators have issued process validation guidelines which emphasize:

- the demonstration of process understanding;
- risk-based identification of critical process parameters;
- implementation of well-validated control strategies.

As a result of the new guidelines, it is now state of the art that drug manufacturers thoroughly investigate and "characterize" the manufacturing processes.

Eljárás karakterizálása – mi a célja, szerepe?

The overall goal of adequate process characterization for commercial manufacturing processes is to ensure efficient and successful validation and the assurance of consistent process performance.

More specifically, For **compliance** the characterization should provide:

- an understanding of the role of each **process step**, such as where impurities are cleared during a particular purification step
- an awareness of the effect of **process inputs** (operating parameters) on process outputs (performance parameters) and identification of key operating and performance parameters
- identify **interactions** between process parameters and critical quality attributes;
- assurance that the process delivers **consistent product yields and purity** in all operating ranges
- **acceptance parameters** for in-process performance parameters.

Eljárás karakterizálása – miért éri meg?

This is a costly and time consuming activity in the product life cycle.

- ❖ *Achieve compliance.* Ultimately, the product should reach the patient. To achieve this, manufacturers must validate the manufacturing process. Process characterization is an integral part of stage 1 process validation.
- ❖ *Avoid registration delays.* A delay in the commercialization of a product has negative impact on patients: They have no access to a drug they can benefit from. Furthermore, a delay in the commercialization costs money.
- ❖ *Avoid failed batches.* Failed commercial batches in biologics manufacturing cost companies millions of dollars. A thoroughly characterized process with the right control strategy in place avoids deviations and failed batches in commercial manufacturing.

Process Characterization Study Deliverables

- A fully defined process with appropriate process controls established.
- Products (product family) covered by the characterization.
- Material limitations (where applicable).
- Measurable process characteristics.
- Identification of Sources of anticipated significant process variation.
- Proposed process controls strategy (recommendations) such as:
 - setup parameters,
 - process instructions,
 - nominal process settings (optimized for “best case”),
 - operating limits of the process identified (anticipated operating ranges including the “worst case” (min/max) settings.
 - actions to be taken if control limits are exceeded

Kontrol stratégia - definíció

Control strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

- **MIT?**

- **MIKOR?**

- **MIVEL?**

- **MILYEN HATÁROK KÖZÖTT?**



Components of Control Strategy that Industry and Assessors Think About

ICH Q10 Control strategy:

A planned set of controls, derived from current product and process understanding that assures **process performance and product quality**.

The controls can include **parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control**.

Pharmaceutical development

QTPP, CQAs

Control of input material attributes *

PARs for CPPs *

Description of manufacturing process *

* Included in Design Space, when applicable

IPC

Justification for non-routine testing, RTRt, predictive models

Regardless of traditional/ enhanced approach (ref FDA-EMA Q/A)

Kontrol stratégia – törzskönyvezési követelmények

Control Strategy

All products **MUST** have a control strategy

Minimal

- ❑ Drug product quality controlled primarily by intermediates (in-process materials) and end product testing
 - QTPP
 - CQAs related to the drug product
 - Appropriate manufacturing process
 - A control strategy

Enhanced

- ❑ Drug product quality ensured by risk-based control strategy for well understood product and process
- ❑ Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
- ❑ **Systematic evaluation, process understanding**
 - Prior knowledge, risk assessment
 - QTPP
 - CQAs, CPPs, Mat CQAs
 - Functional relationship between CPPs, Mat CQAs and CQAs with related ranges
- ❑ **Establishment of design space - optional**
- ❑ **Enhanced Control Strategy (eg PAT, TRT)**
- ❑ **Continual improvement**



Kontrol stratégia elemei

Gyártás

ELŐTT

I. Input material controls for DS and DP manufacture

- Risk assessment and qualification
- Raw materials, excipients, primary packaging materials

KÖZBEN

II. Process control elements

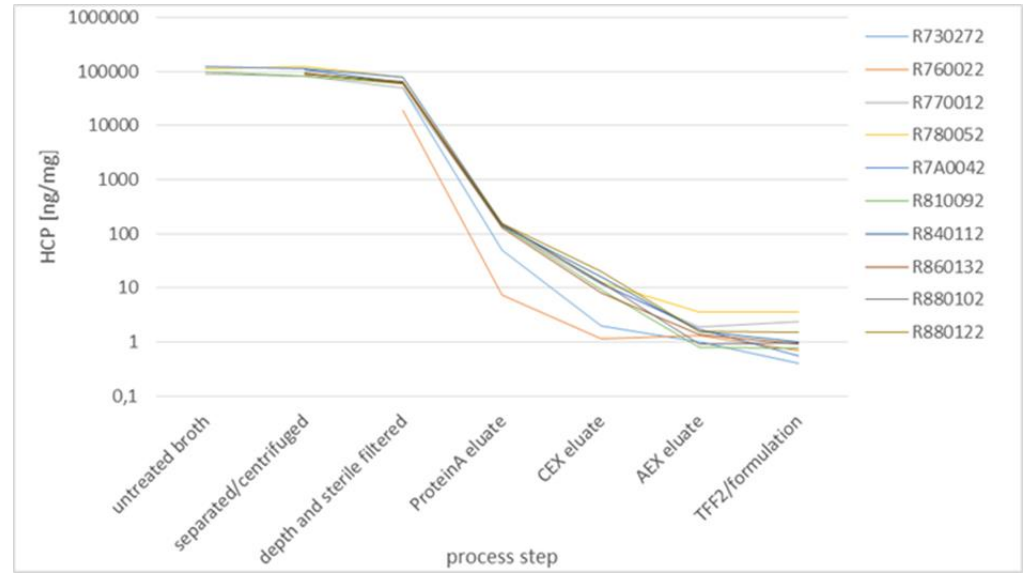
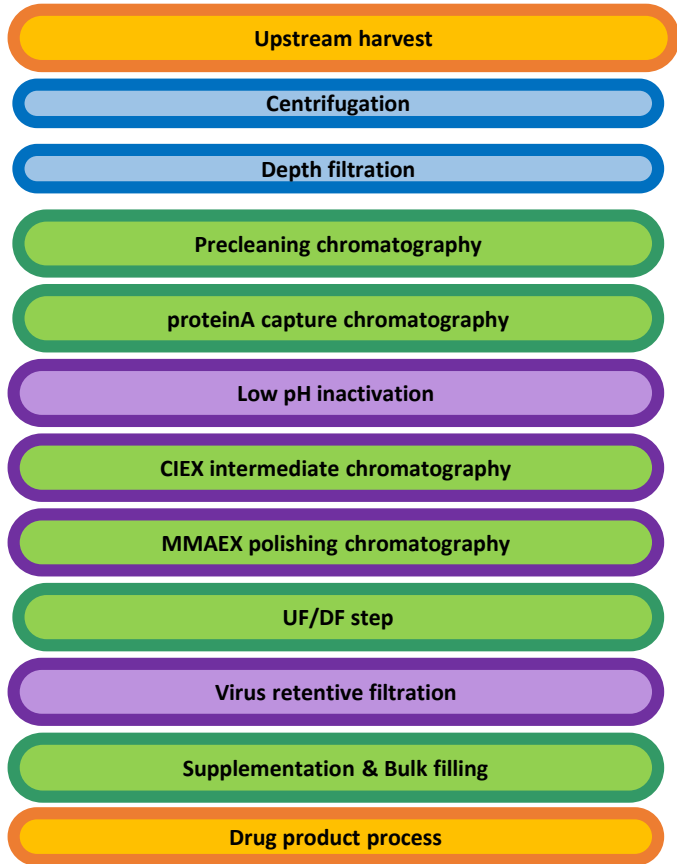
- Procedural controls
 - Facility
 - Equipment
- Process parameter control
 - CQA, QTPP, CPP, non-CPP, process validation exercise

UTÁN

III. Testing control elements

- Cell line characterization
- Genetic stability
- Viral clearance studies
- Resin lifetime studies
- In-process testing
- Hold times
- Shelf life and stability
- Bulk harvest test
- Specifications
- Reference to stability program
- Comparability
- Process monitoring (testing and evaluation)

Case study 1.



	HCP	HCDNA	LPA	IEX			SEC		N-Glyc.		criticality
				AV	K1+K1'	OBV	HMW	LMW	MAF*1.9 +	HM	
Weight	10	10	10	3.3	3.3	3.3	5	5	5	5	criticality
Process Step											
MSP	9	9	9	0	0	0	0	0	0	0	270
CEX	3	0	9	3	3	9	9	0	0	0	215
AEX	3	0	0	0	0	0	3	0	0	0	45
formulation	0	0	0	0	0	0	0	0	0	0	0
positive effect	15	9	9	3	0	9	12	0	0	0	
negative effect	0	0	9	0	3	0	0	0	0	0	

Case study 2. - Üzemi vírusfertőzések

Raw materials as a source of contamination in large-scale cell culture

Article in *Developments in biological standardization* 93:21-9 · February 1998 with 107 Reads
Source: PubMed

Genentech,
1993/1994
CHO, MVM,
RT-PCR

Genzyme Detects Virus Contamination of Bioreactor, Halts Production

Jul 2, 2009

Jun 17, 2009 By Laura Bush

Genzyme Plant Shutdown Could Mean up to \$300M in Lost Sales

Sales of drugs for Fabry, Gaucher's, and Pompe diseases will take a hit.

Global Vaccine Safety

Porcine circoviruses and rotavirus vaccines

Extract from report of GACVS meeting of 16-17 June 2010, published in the WHO Weekly Epidemiological Report on 23 July 2010

Genzyme,
2008, BEL,
2009 MA, USA
CHO, Vesivirus 2117
RT-PCR

GSK,
2010.03, Rotateq
PCV-2 DNS
végső kisherelésben és
„bulk”-ban

Merck,
2010.05, Rotateq
PCV-1 DNS
MCB, MVS



A vírusbiztonság három „pillére”

Vírusmentesség

Nyersanyagok

Monitorozás

Eltávolítás

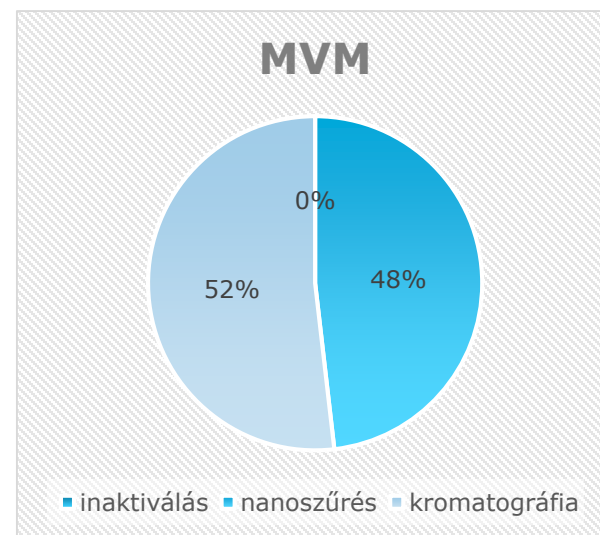
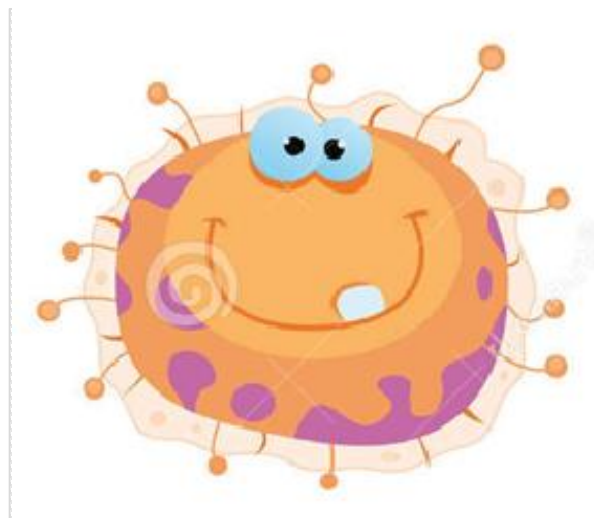
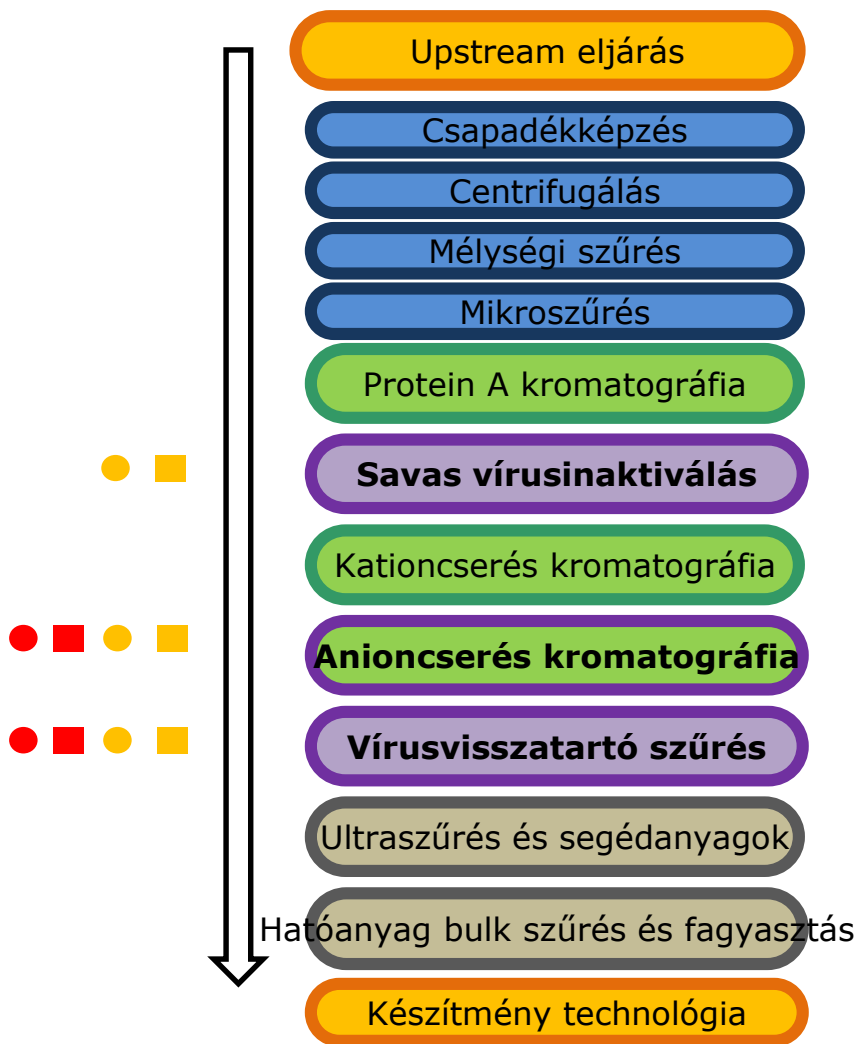
- MCB/WCB karakterizálás
- *In-vivo* tesztek
- HAP/RAT/MAP
- RT-PERT esszé
- TCID esszé
- TSE/BSE
- Endogén vírus

- Bulk harvest teszt
- Purified bulk teszt
- TEM

- Szolvens/detergens
- UV-C inaktiválás
- Savas inaktiválás
- Nanoszűrés
- Spike-and-Run
- Specifikus modell vírus
- Nem specifikus modell vírus
- Jellemző modell vírus

Vírusbiztonság – viral clearance rész

- MuLV
- PRV
- MVM
- Reo-3



K+F labormenedzsment

Benkő Zsuzsa, Sütő Zoltán



Personal take home message

Hard Skills

Teachable abilities or skill sets that are easy to quantify.

你好吗?

Proficiency in a foreign language



A degree or certificate



Typing speed



Machine operation



Computer programming

vs.

Soft Skills

Also known as "people skills" or "interpersonal skills."



Communication



Flexibility



Leadership



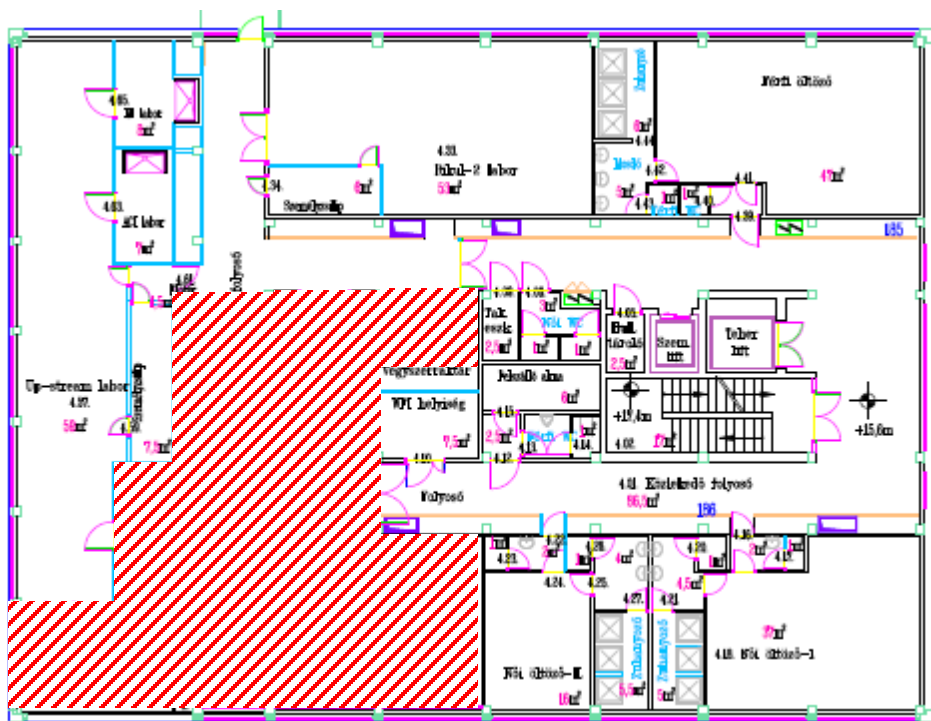
Teamwork



Time Management



Laborterület és berendezések



	Type	Capacity	Count	Vendors
Laboratory scale chromatography systems	FPLC	10-100ml/min	6	
Pilot scale chromatography systems	FPLC	24-600L/hr	3	
Laboratory columns	Borosilicate glass	0,66-5cm	50+	
Pilot columns	Acrylic	5-80cm	12	
Depth filtration	mainly Capsule & Lenticular	22cm2-1,6m2	3	
Normal Flow filtration	Capsule & Cartridge	150cm-2,5m2	NA	
Off-line sensors	UV-VIS, Turbidity, pH, Conductivity, DO & RedOx	NA	appr. 10	
Mixing systems	Single use, wand mixers	10L-1000L	7	
	SS vessel	50-100L	5	

Ellátórendszerek:: hőmérséklet kontroll, E11 légszűrő 95% >0,5µm visszatartás, 2-8⁰C hidegszoba és hűtők, -20⁰C fagyasztók, szeparált anyag és személyzilip

Debreceni Biotechnológiai Üzem

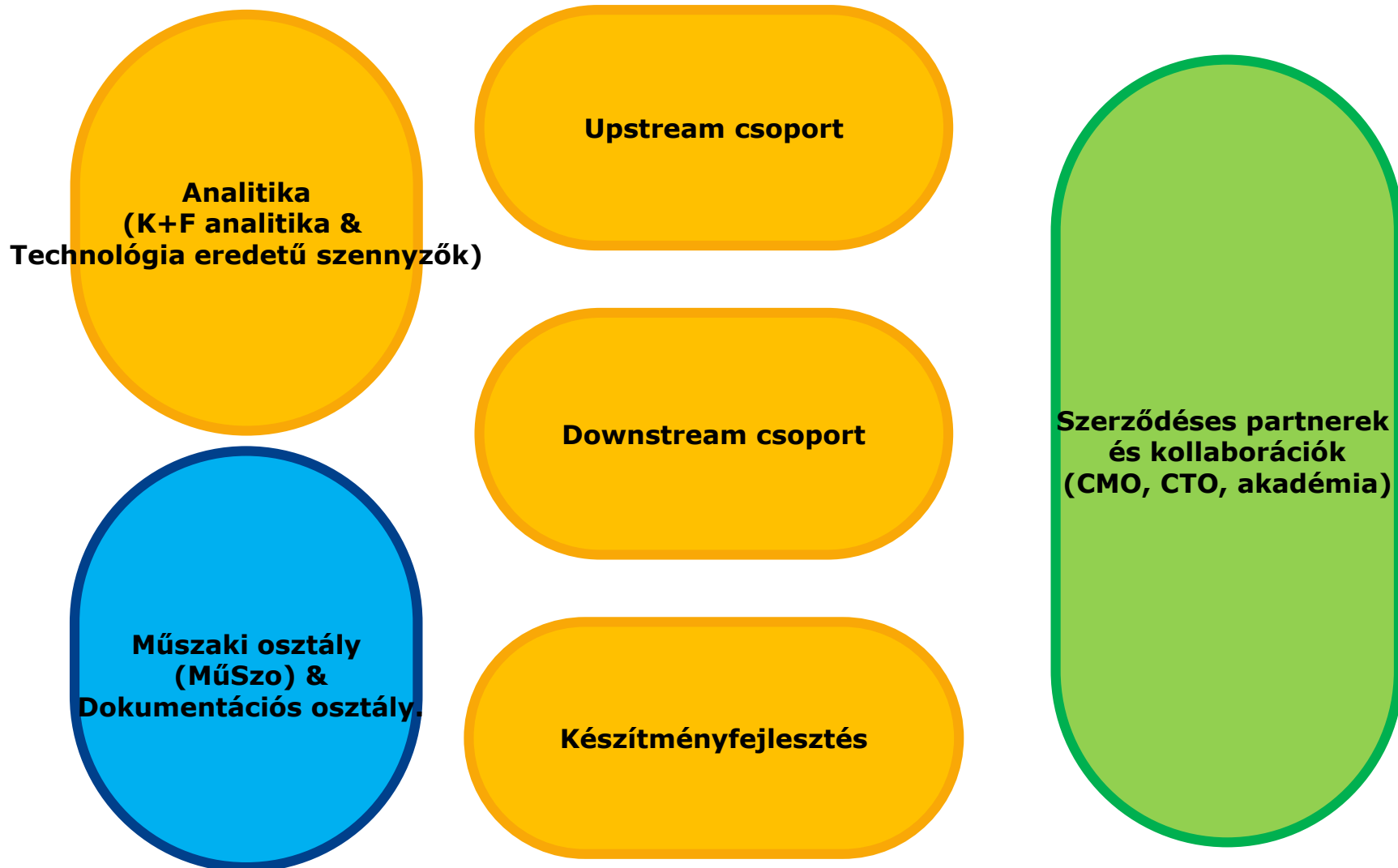
**Üzembe helyezés: 2012.
Zöldmezős beruházás
Folyamatos bővülés**



- Emlősejt-tenyésztés & downstream feldolgozás (DS)
- Készítményfejlesztés és gyártás (DP)
- Analitikai támogatás
- **2 x 5000 l SS & 4 x 2000 l SUB bioreaktor kapacitás**
- **2 x 50 l pilot léptékű bioreaktorok**
- Jelenleg klinikai vizsgálatra gyártások
- CMO tevékenység
- K+F MBL labor

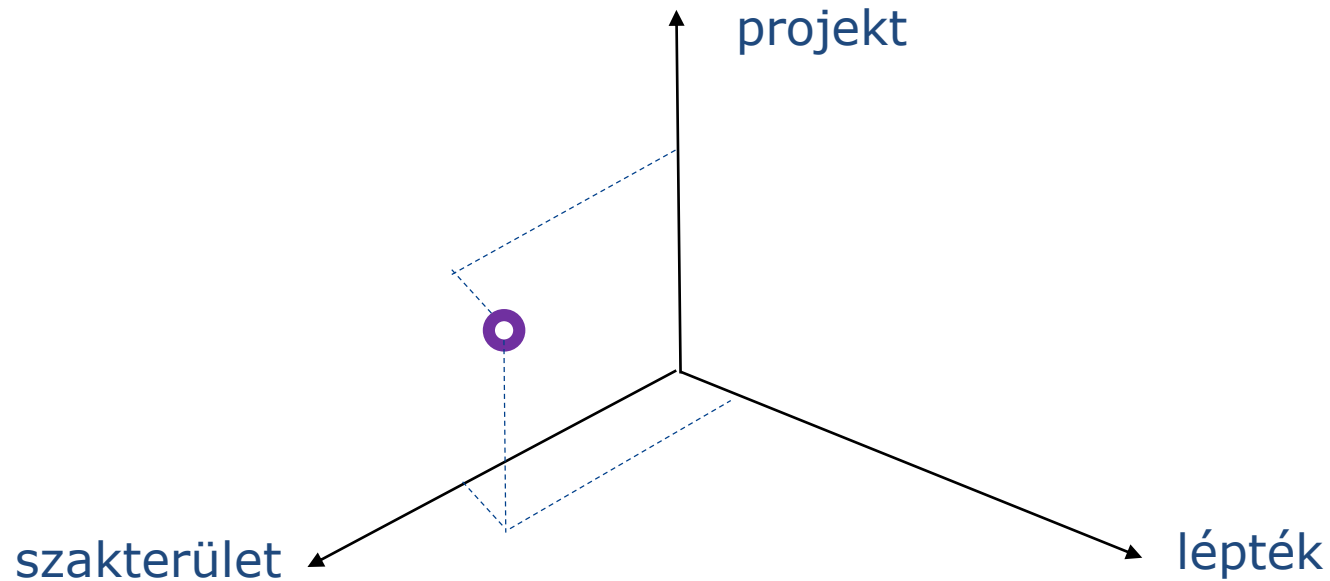


Működési környezetünk



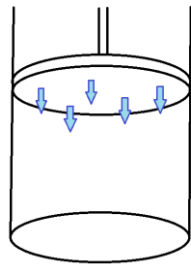
Technológus feladatkörök

Laci	RGB-09	RGB-08	VC	RGB-14	RGB-17
Viktor	RGB-09	RGB-08	HTS	RGB-14	
Balázs		RGB-08	RGB-02	RGB-14	RGB-19

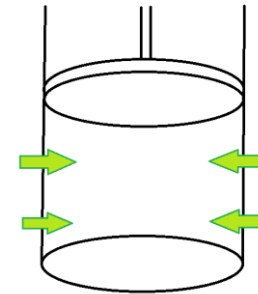


Technikusok 1. - Előkészítő műveletek

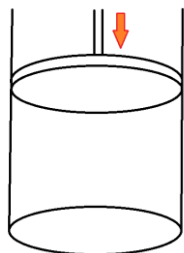
Töltés áramlással (flow packing):
(stall packing):



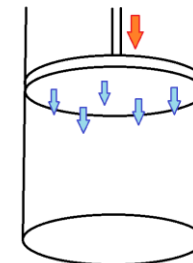
Fix magasságú töltés



Axiális kompresszió (axial compression):
kompresszió (DAC):



Dinamikus axiális



Technikusok 2.

Tóni
Nelli
Gyuri








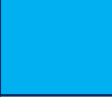

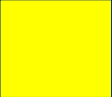
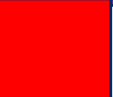

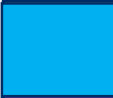




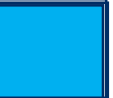
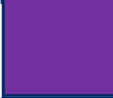




















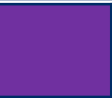








Győző
Kati
Robi

laborműszerfelelős, GMP műszakvezető
vegyszer és eszközrendelések
pilot és üzemi berendezés felelős, GMP
műszakvezető
belső raktár kezelés
labor és irodai berendezés leltár
automata pipetták kezelése

	A	B	A	B
KA	DE (7-15)	DU (13-21)	DE	DU
GyGy	DE (7-15)	DU (13-21)	DE	DU
GGyu	DU (14-22)	DE (6-14)	DU	DE
PR	DU (14-22)	DE (6-14)	DU	DE


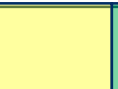






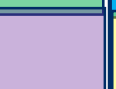







































Feladatokról – személyekre bontva

	Juliska
	Géza
	Lajos
	Éva
	Reni
	Béla

Feladatokról – időben szűkítve

	Juliska
	Géza
	Lajos
	Éva
	Reni
	Béla

Priorizálás - projektcélok

I. RGB-10 <= \$\$\$

II. RGB-02
1. PEG minősítés
2. KO36 elszíneződés
3. KO82 As és KLKT kritériumok

III. RGB-14
1. laborléptékű kromatográfia
2. formulálási lépések (TFF-VF-F&T)
3. léptéknövelés
4. üzemelés

IV. RGB-08
1. III. 5000L hatóanyag gyártás
2. működési tartományok meghatározás lezárása
3. folyamat-validálás elindítása
4. laborléptékű folyamat-validálások (?)

V. RGB-03

VI. 1. tudományos tanácsadástól függ

RGB-17
DSP fejlesztés támogatás

További célok

A projektfeladatokon túl:

- Technológus tehermentesítés
- **Belső folyamatok javítása** (oktatási mátrix)
- GMP gyártás, problémák megszüntetése
- **Hibák minimumon** tartása
- Eszköz-, vegyszerkészletek naprakészen, berendezés állapota
- Dokumentációs visszakövethetőség és **adathűség** papírforma és elektronikus (ELN)

+

Új eszközök berendezések (TECAN és HTS megközelítés)

=

- Szellemi termékek pl.: szabadalom
- Niche témékeket célozva
- „Tonnaháborútól” való eltávolodás
- Fejlesztés és exploráció arány eltolása exploráció irányába

Csoport perspektíva - újratervezés

RGB-08	RGB-14
Karakterizáció	Labor és pilot feldolgozások

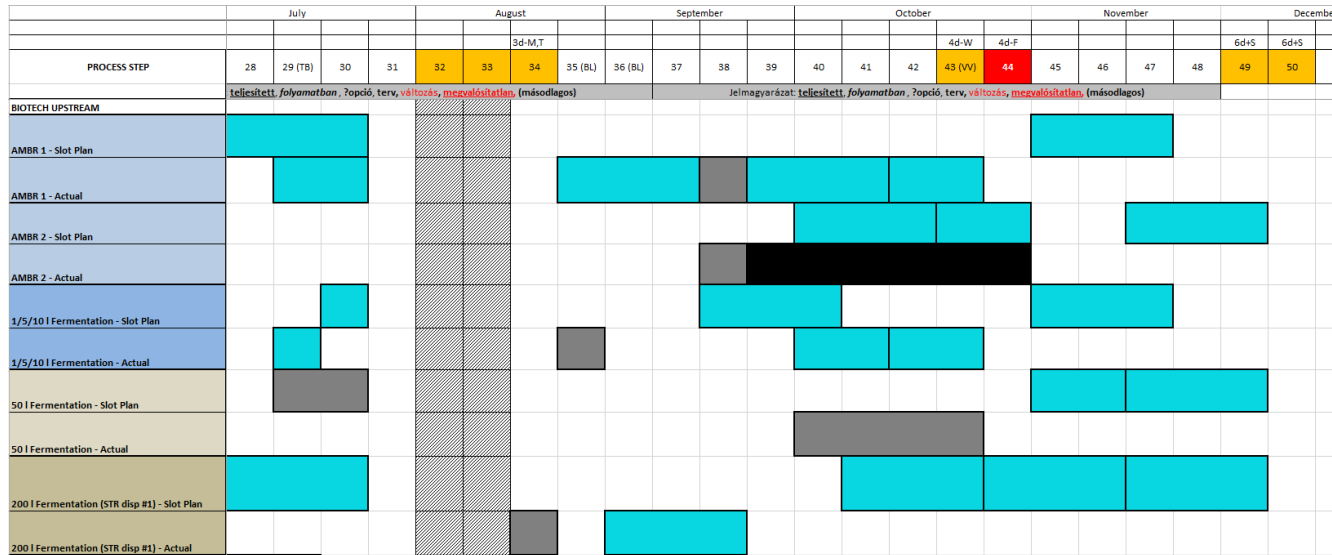


HTS exploráció	RGB-14
HTS karakterizáció	Lincense-in projekt?
RGB-14 karakterizáció	Labor és pilot feldolgozások
Coli projektek támogatása	Kollaborációk

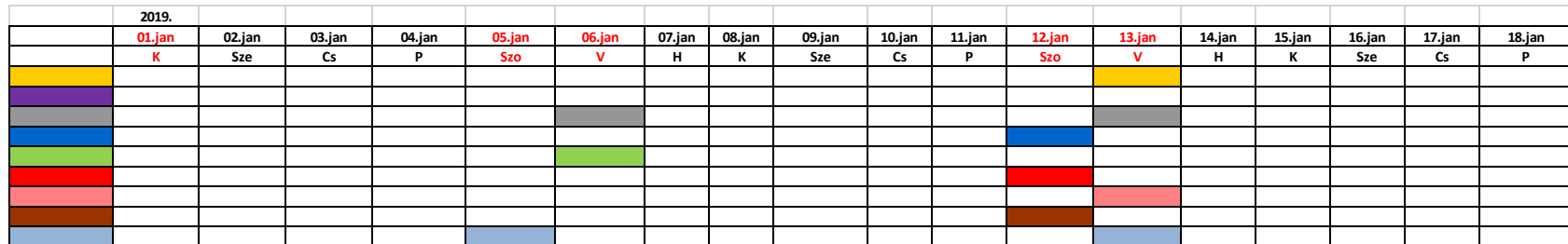
a kapacitásainkat több kisebb feladatból kell feltölteni, külsős feladatok és több menedzsment igénnyel párosul

Tracker tools

- Slot plan



- Staff schedule



- Task tracker



Formulation challenges

Kollár Éva





KÖSZÖNJÜK A FIGYELEMET!

Elérhetőségeink:

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Kollár Éva (E.Kollar@richter.hu)

Sütő Zoltán (Z.Suto@richter.hu)

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