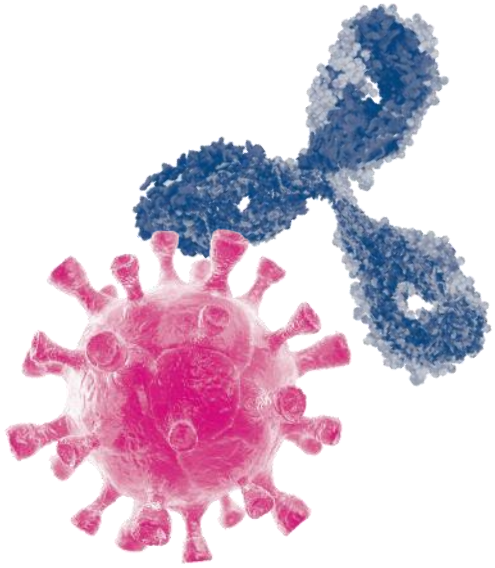
HALIX

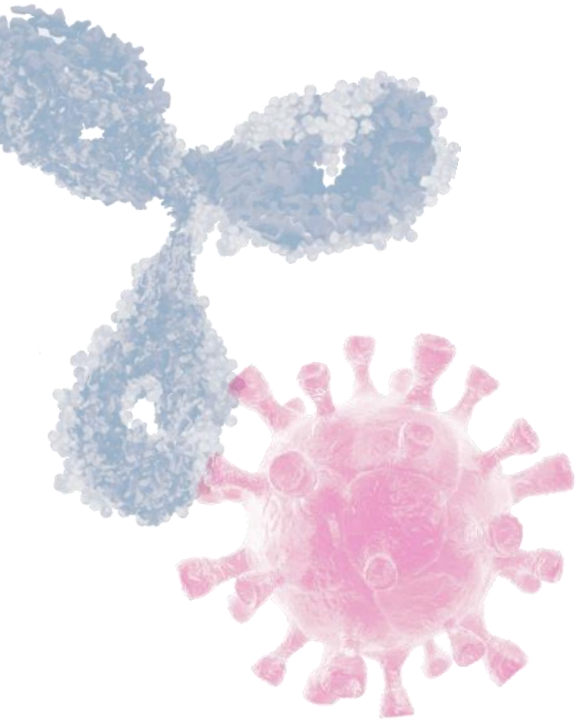


BIOSCIENCE AS A SERVICE

R&D and Product Launch to commercialization

Dutch Life Science Congress
November 2019

Agenda



Overview HALIX

CDMOs during clinical phase

Case study 1: Virus Manufacture

Case Study 2: Protein Production

HALIX’s new facility

Continuous growth in a strong corporate structure

1959: HAL Allergy was founded in Haarlem

2002: Acquired by Droege Int. Group

2009: Relocation Head Office to Leiden Bio Science Park

2011: Start CMO services within HAL Allergy

2012: Launch of HALIX B.V.

2018: Start construction activities of new building

2019: Inauguration of state-of-the-art cGMP facility

The end-to-end service for your product

HALIX
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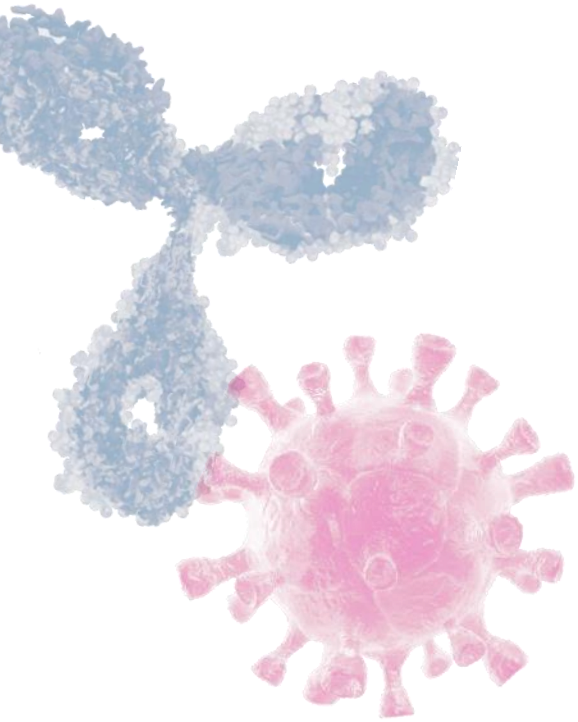
Service Portfolio

Development

GMP Manufacturing

Complementary

Agenda



Overview HALIX

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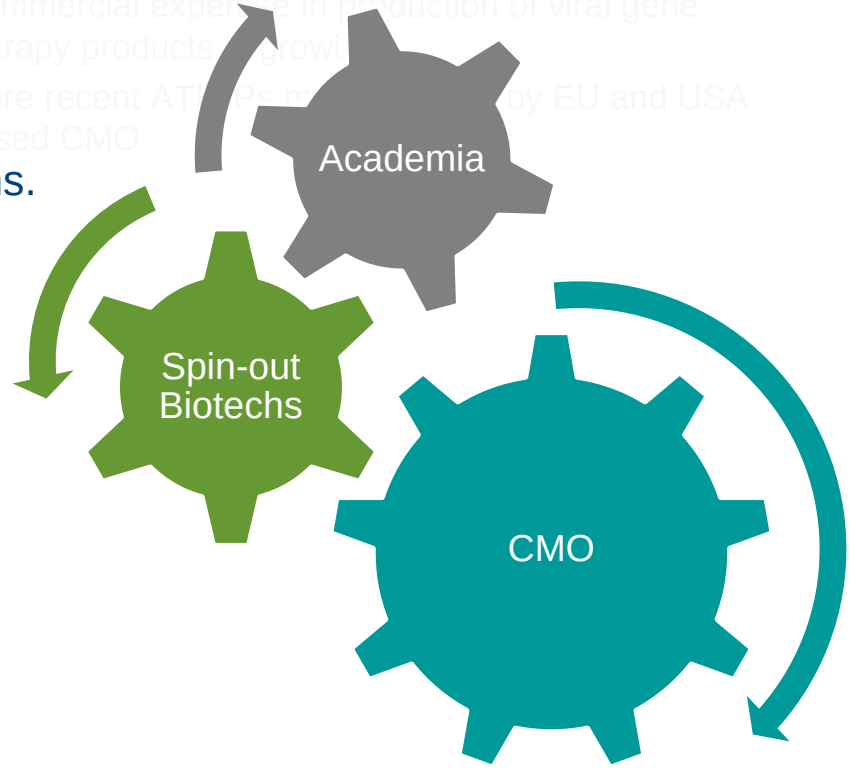
Partnership between stakeholders is critical to success

Combined expertise

- Academia which invents new options
- Spinout Biotechs which take ownership of these inventions
  - Scientific understanding
  - Product related expertise
- C(D)MOs safely and reliably produce these inventions.
  - Multiple projects performed
  - Seen pitfalls and successes
- Shared interest in successful project.
  - Shared project team
  - Open communication
  - True partnership



When can we help you with what?

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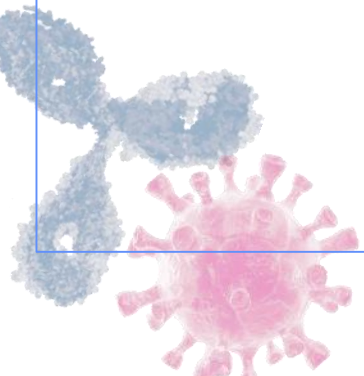
Technology development

- Start talking
- Slot reservation?
- Process evaluation
  - Manufacturable
  - Scalable?



Pre-clinical

- Process development & scale up
- Assay development
- Setting your specs
- Engineering batches
  - Tox material
  - Standards

Phase 1

- MCB / MVS
- Lock down protocols!
- GMP DS and DP manufacture
- Assay qualification
- GMP stability studies
- Viral clearance (ph1)

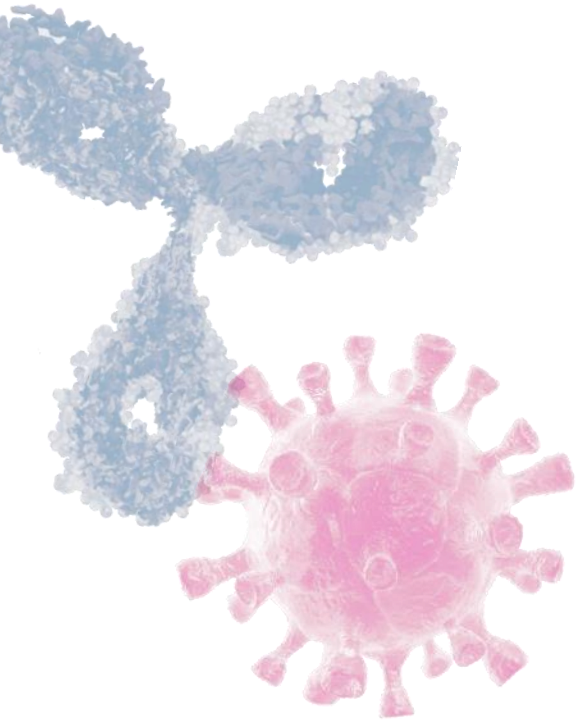
Phase 2

- Scale up
- WCB / WVS
- Is your CDMO your partner for the future?
- Is your process ready for commercial? (COGS / Assays /Formulation / presentation (lyo?)

Phase 3

- Scale up to production size
- Process validation (!!)
- Assay validation
- Viral clearance (ph3)

Agenda



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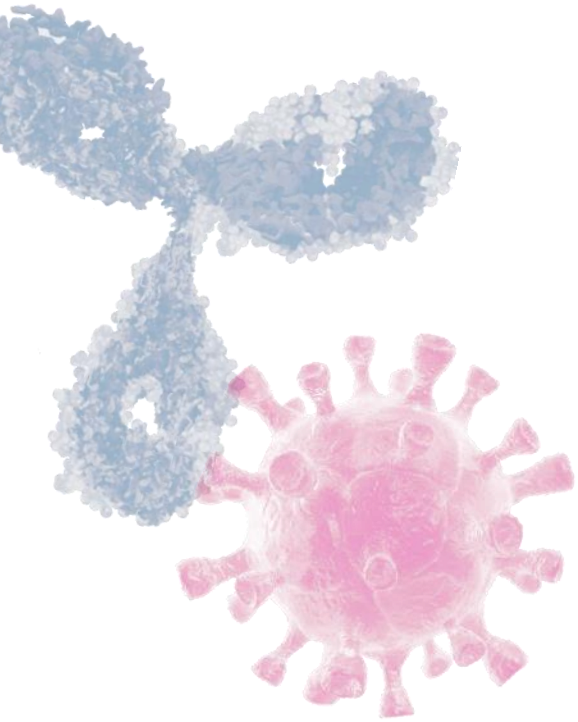
Case study 1: Virus Manufacture (1)



- Small biotech, founded by seasoned experts
- Cancer vaccine
- 2 viruses (prime and boost)
- VERO cell line (adherent) supports robust growth
- Simple yet efficient DSP (Benz / TFF / Chrom)
- Phase 1 batch of each virus requested

Timeline & project overview

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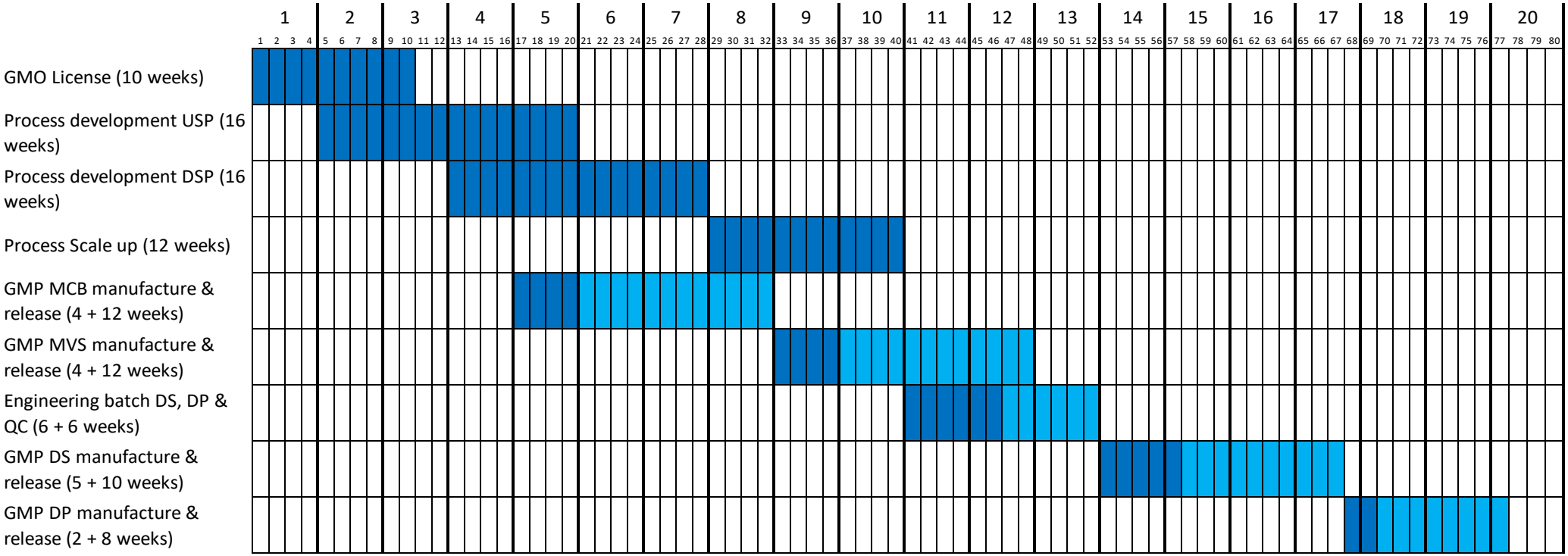
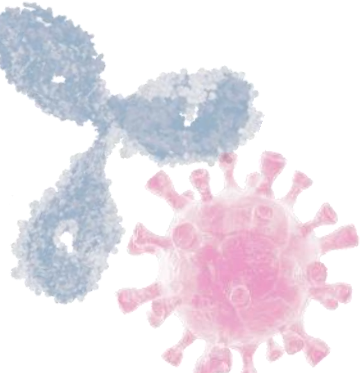
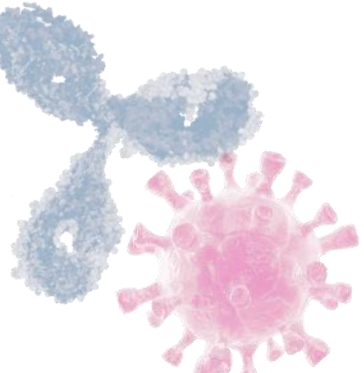




Case study 1: Virus Manufacture (3)

- USP yield: 10E8-10E9 particles / ml
- Process contaminants (hcDNA HCP etc) reduction > 95%
- Drug substance: 50 times concentration of infective virus particles compared to BDS
- Final DP manufacture → simple dilution and FF.



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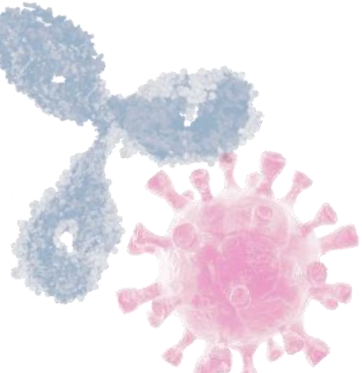

Case study 1: Virus Manufacture (4)

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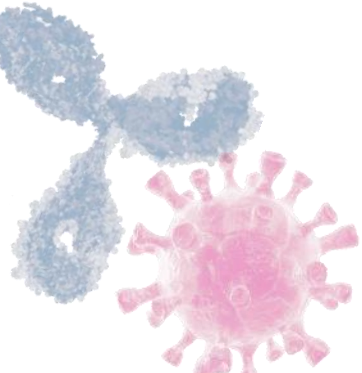
- But…

- During engineering runs
    - Genetically instability suspected in one virus seed
    - Extended culturing confirmed, MVS not stable!



Case study 1: Virus Manufacture (4)

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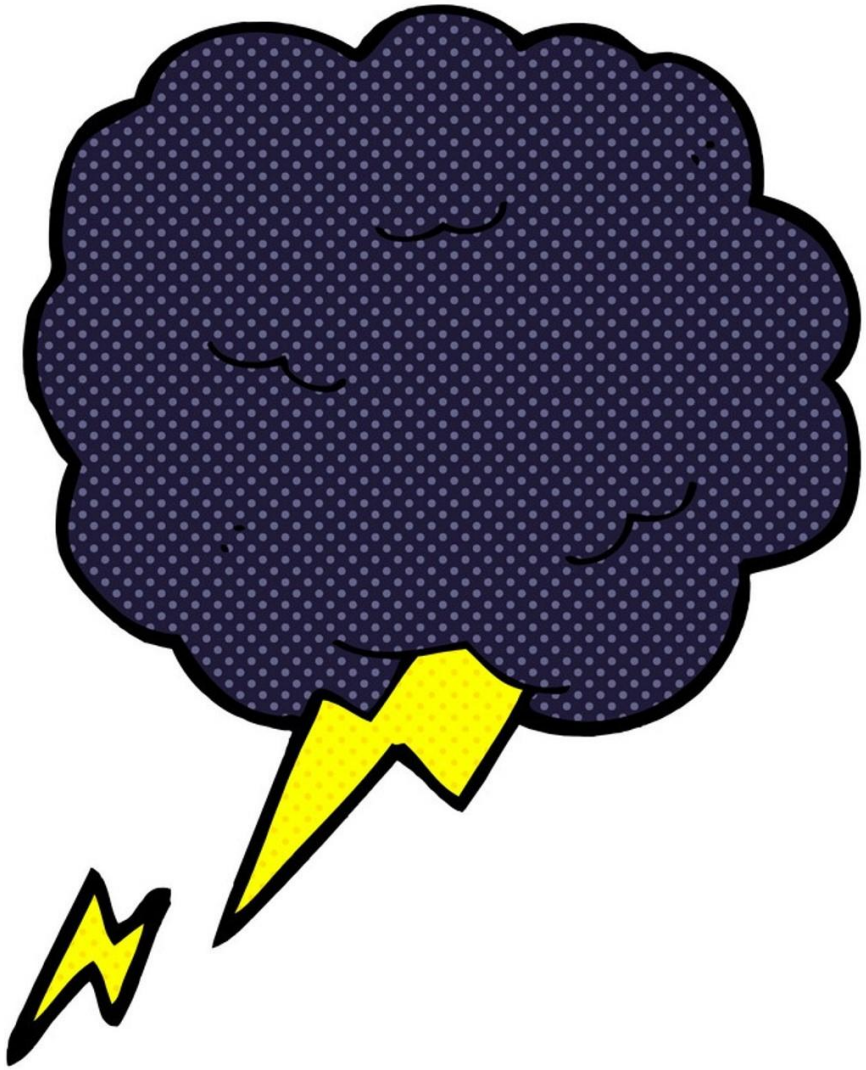
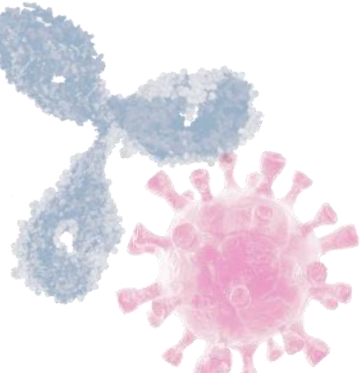
- But…

- During engineering r
  - Genetically
  - Extended cu





Case study 1: Virus Manufacture (5)

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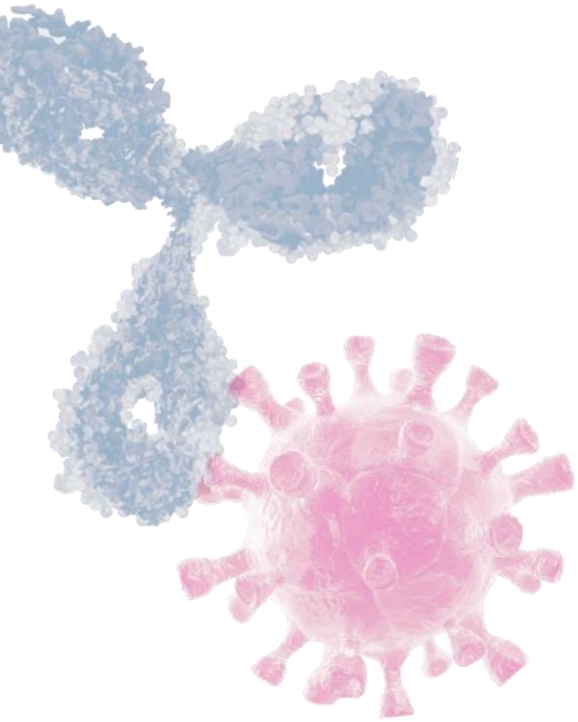
Solution lies in open communication and close collaboration!

- Re-planned production strategy & timelines to focus on other virus
  - Process designed to work for both viruses
- Reassigned planned production slots to other program
  - Minimal cost for slot cancelation
- Phase 1 trial initiated with stable virus
- 12 months later→ produce second (booster) virus (from new, genetically stable rVS)
- **In the end no time lost for customer & total additional CDMO costs < 100K**

Agenda



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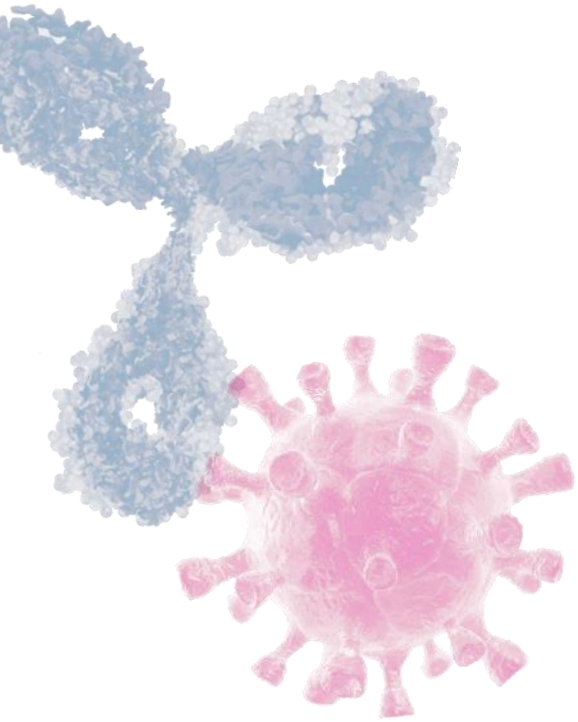
HALIX's new facility

Case study 2: Protein Manufacture (1)



- Antibody variant (not MAb) for cancer indication
- Stable but Low yield
- High efficacy
- Phase 1 manufacture
- No stable cell line available
- Product binds to Protein A (Downstream process)

Time to phase 1 material (Protein product)

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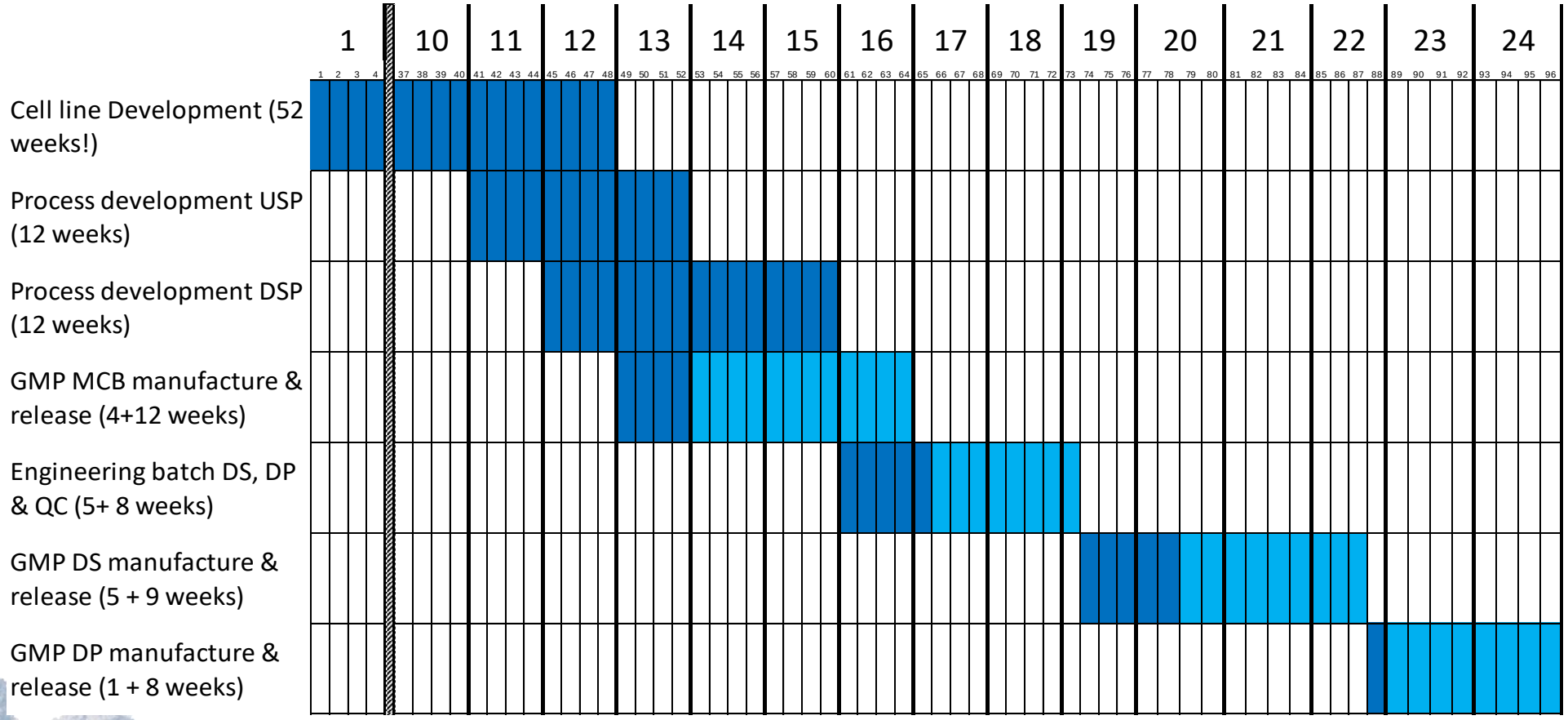

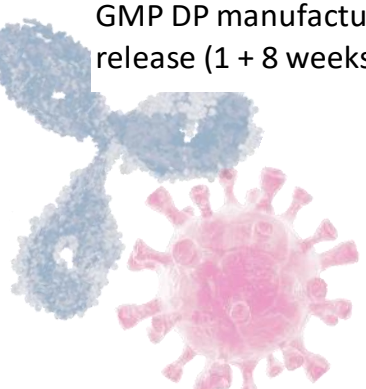

Case study 2: Protein Manufacture (2)

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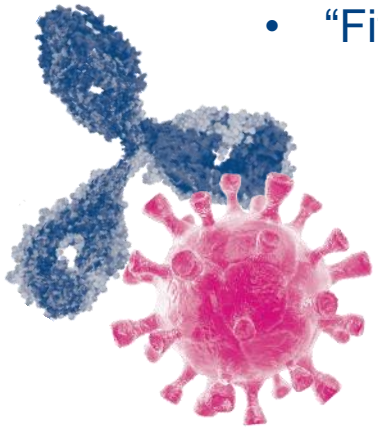
- University spinout
- Customer needs to initiate Ph1 rapidly, cannot wait 2 years for Ph I GMP material
  - Needs to meet milestone planning to unlock funding
- Transient transfection strategy!
  - HEK 293 cells (commercially available as GMP bank)
  - 20-40 CF 10 flasks
  - “Fit for purpose” DSP strategy



Case study 2: Protein Manufacture (3)

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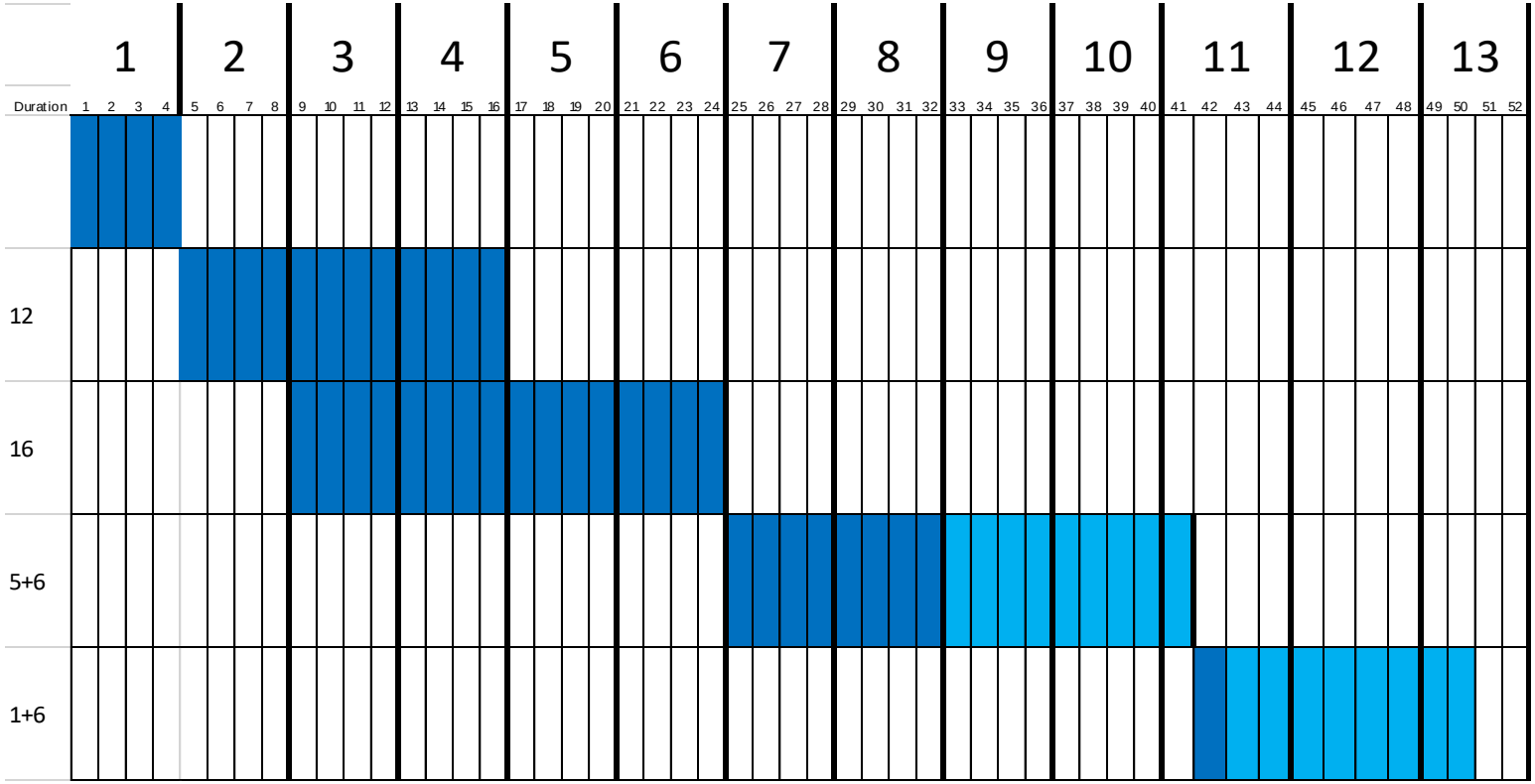

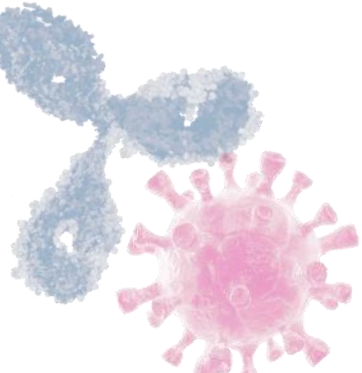

Case study 2: Protein Manufacture (3)

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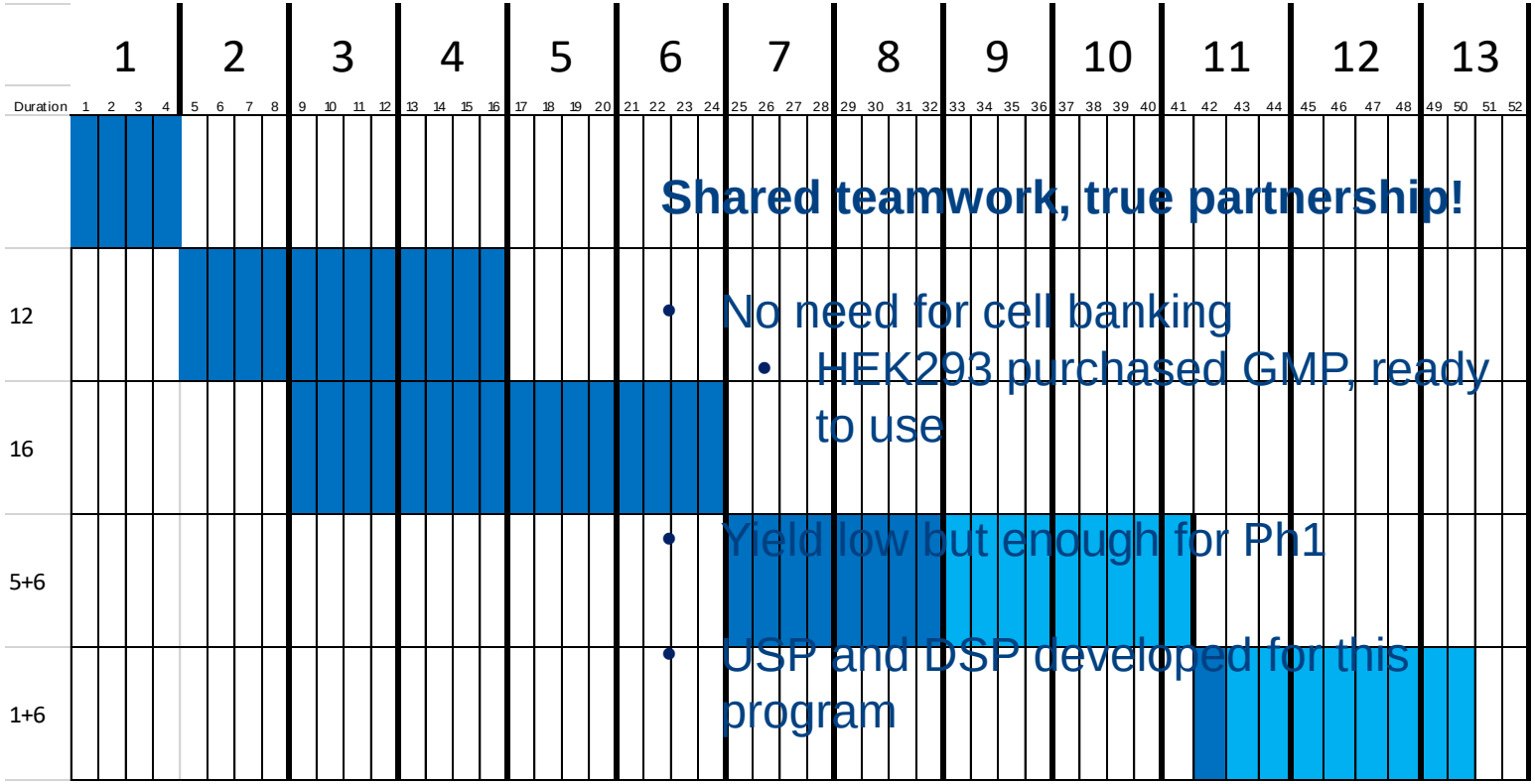
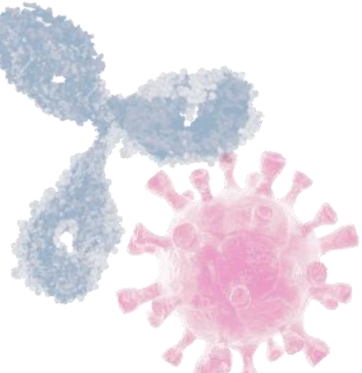


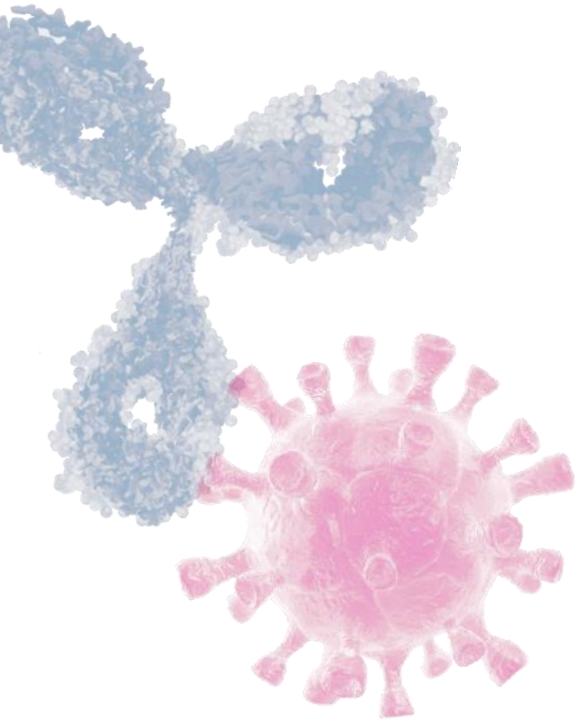
Shared teamwork, true partnership!

- No need for cell banking
  - HEK293 purchased GMP, ready to use
- Yield low but enough for Ph1
- USP and DSP developed for this program

- Total timeline from intiation to FDP release aprox 12 months.



Agenda



Overview HALIX

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HALIX's new facility

New Production Facility HAIX in the LBSP

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Construction details on the new LSBP CDMO facility

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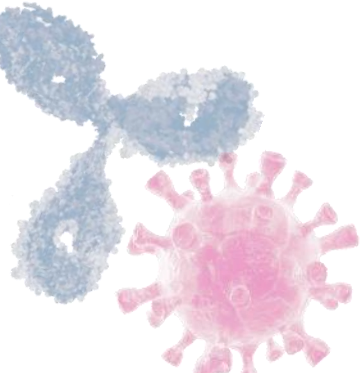
General Facility Data

- **Construction Building**
  - > Construction designed for industrial use (5 layers)
  - > Maximal floor load 2,000 KN/m2
  - > Equipped and prepared for future expansion
  - > 1,300m^2 floor space per layer

- **Design Compliance**
  - > Pharmaceutical: EU / FDA guidelines
  - > Containment BSL2/3: Dutch law, NIH



State-of-the-art cleanrooms and GMP production capabilities

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Technical Details – New Facility

- **Clean rooms**
  - > **Flexible**:
    - > Single projects and commercial manufacturing
  - > **Box in box principle**
    - > Maintain stable climate in each cleanroom
  - > **Compliant**
    - > Separate air treatment for each cleanroom
    - > Uni-directional flow of personal and material
  - > **Safe**
    - > Decontamination using fumigation systems
- **GMP Production Capacities**
  - > 1,000 L single use bioreactors in grade BSL2
  - > 250 L single use bioreactors in grade BSL2

Grand opening of building 21 November 2019

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