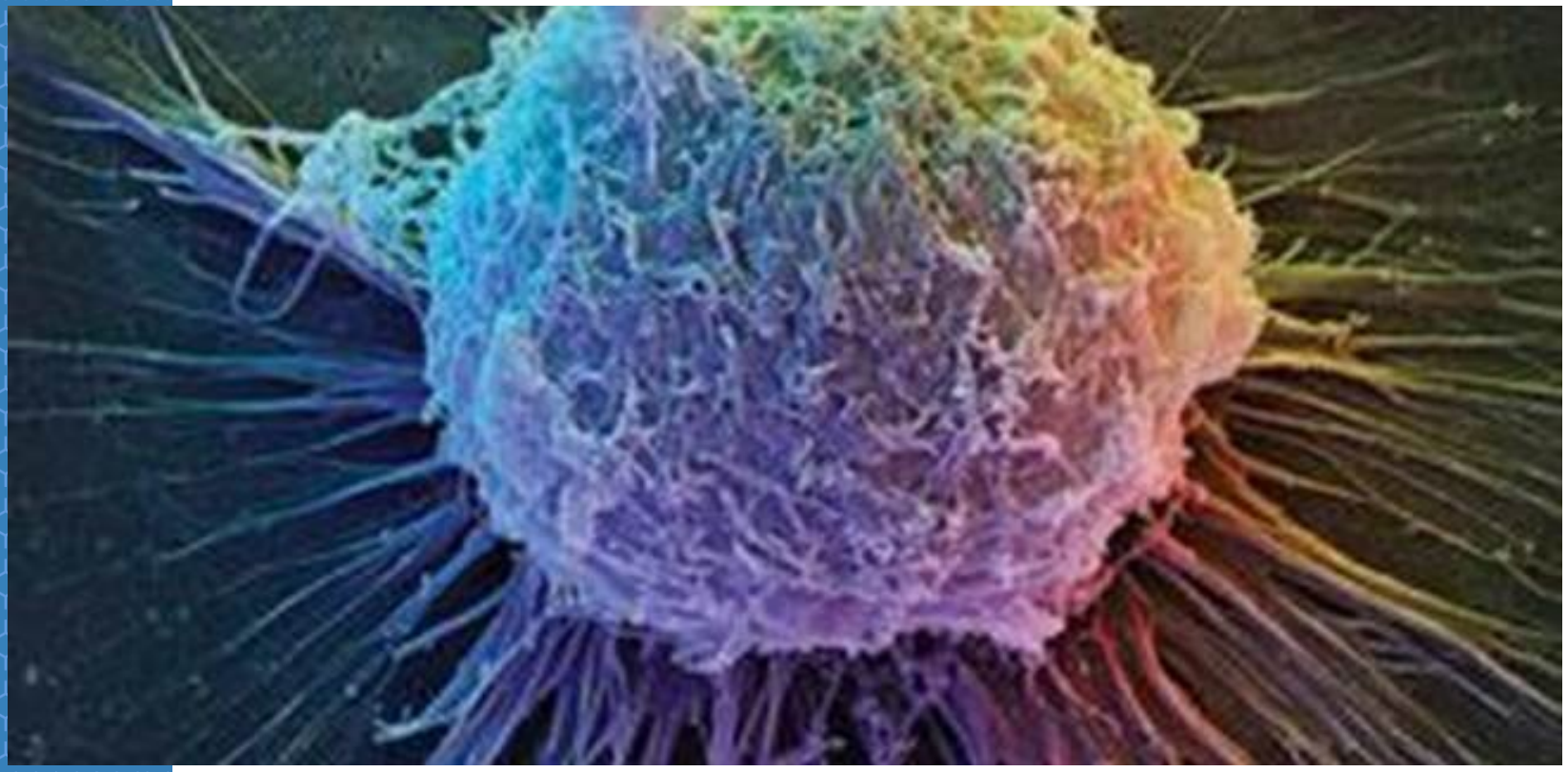

Lifecycle Management: Challenges and Lessons Learned from Kymriah™ (CD19 CAR T)

Anthony Thatcher, Site Head MS&T
Novartis Pharmaceuticals Cell and Gene Technical Development and Manufacturing
July, 2018

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Agenda

Kymriah™ (CD19 CAR T) Overview

Early Development and Transfer

Characterization and Process Development

Process Validation and Launch

Challenges / Lessons Learned

The Next Chapter of Kymriah™

Novartis CTL019 CAR-T Cell Therapy

Hospital / Infusion / Apheresis Centers

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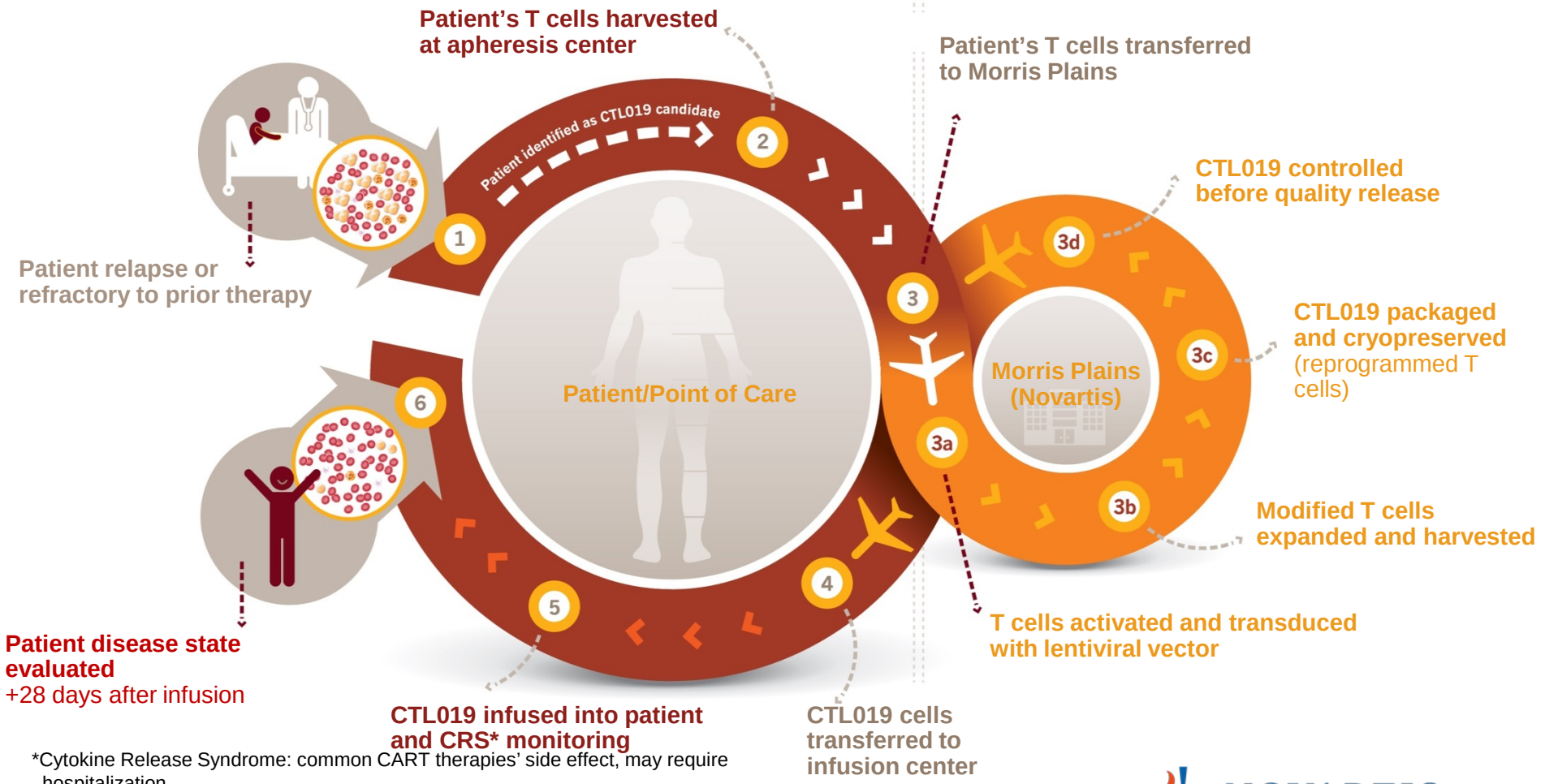

*Cytokine Release Syndrome: common CART therapies' side effect, may require hospitalization

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Early Development and Transfer

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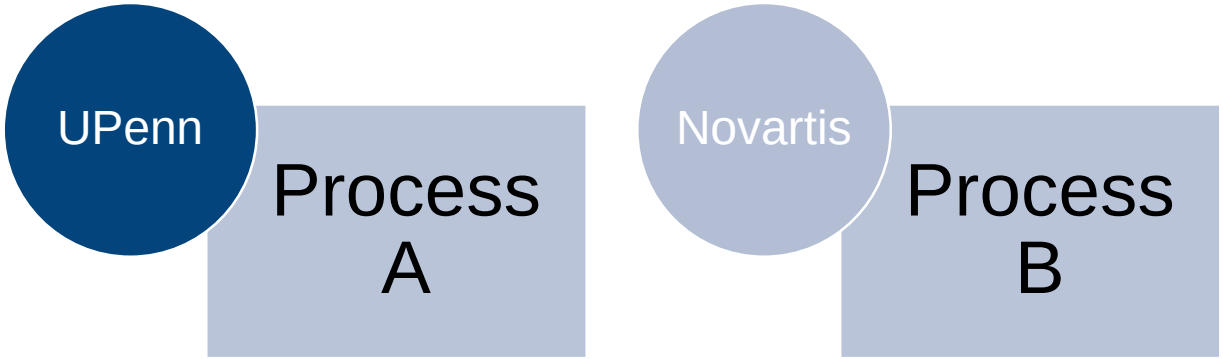
Early Clinical Development Historical Timeline

Year	Learning	Reference
1997	CD3/CD28-bead costimulation for CD4+ T cells	Levine at al. JI 159:592
1998	Large scale production of CD3/CD28 costimulated CD4+ T cells	Levine et al. J Hematotherapy 7:437
2000	CD4 and CD8 respond differently to CD3/CD28 costimulation; double positives sign of immuno senencensce	Laux et al. Clin. Immunol. 96:187
2002	Adoptive transfer of CD3/CD28 costimulated CD4	Levine et al. Nat. Med. 8:47
2003	GMP Bioreactor-based process for autologous T cell therapy	Hami et al. BioProcess J 2: 23 (Xcyte Therapies)
2004	CML remission post CD3/CD28 costimulated autologous T cells	Rapoport et al. BM Transplantation 33:53.
2006	DLI with allo donor cells expanded with CD3/CD28 costimulation; CD14 depletion >20% monos	Porter et al. Blood 107:1325
2011	Autologous CAR+ T cells for anti-leukemic memory	Kalos et al. Sci Transl. Med 3:1
2011	CAR+ T cells in CLL	Porter et al. NEJM 265:725.
2012-2014	Tech transfer from UPenn to Novartis	Novartis documents

Key Considerations in Kymriah™ During Transfer

- Transfer + Process Improvements
- Open systems to closed where feasible
  - Water bath to Plasmatherm
  - Open Product Transfers to Luer Connections
  - Open bead wash step to closed process
  - Replace Luer Connections wherever possible with tube welding
- Manual to automatic
  - Manual Ficoll to automated Sepax



Process Transfer

Evaluation

- Feasibility (Process A)
- Quality Risk Assessment
- Alternatives
- Selection of Receiving Site

Planning

- Team formation and kickoff
- Regulatory assessment
- Manufacturing process transfer protocol

Preparation

- Documentation packages
- Training
- Incorporation of Process Improvements

Process Transfer (cont)

Execution

- Feasibility Runs (test)
- Engineering Runs (confirm)
- Comparability Runs (regulatory)

Assessment

- Analysis of results
- Submission of comparability data
- Manufacturing process transfer report

Post-transfer

- Lessons learned
- Initiate monitoring
- Phase 2 clinical trial at Morris Plains
- Begin process characterization (Process B)

Characterization and Process Development

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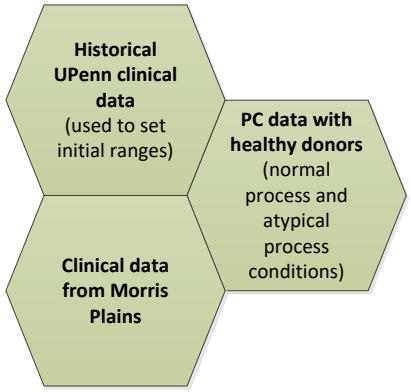
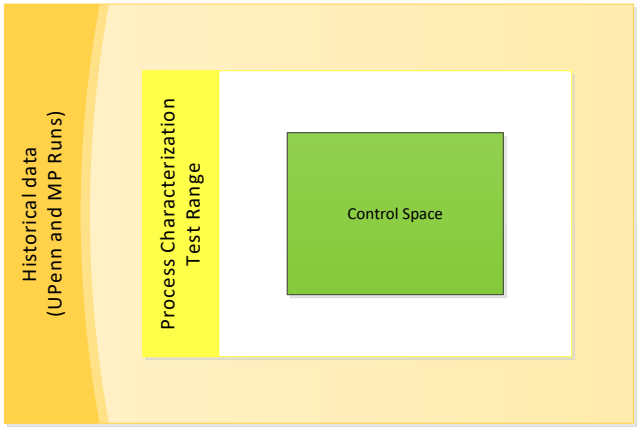
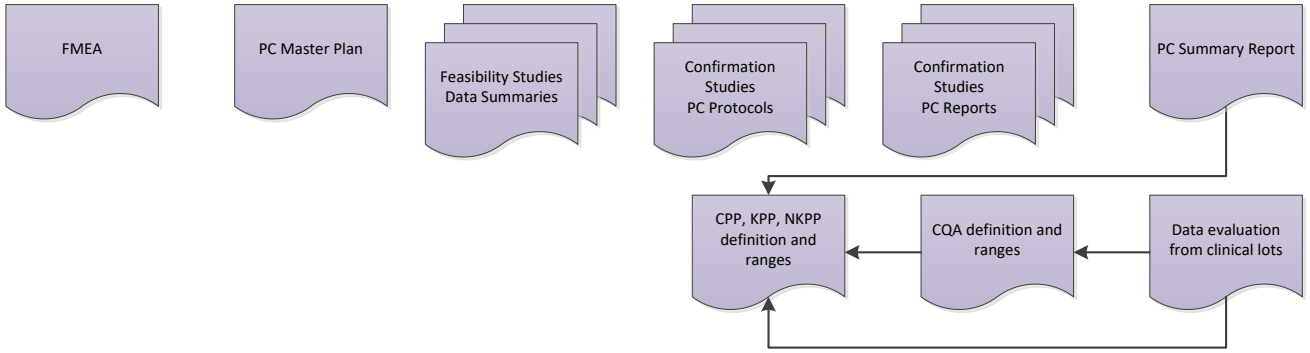
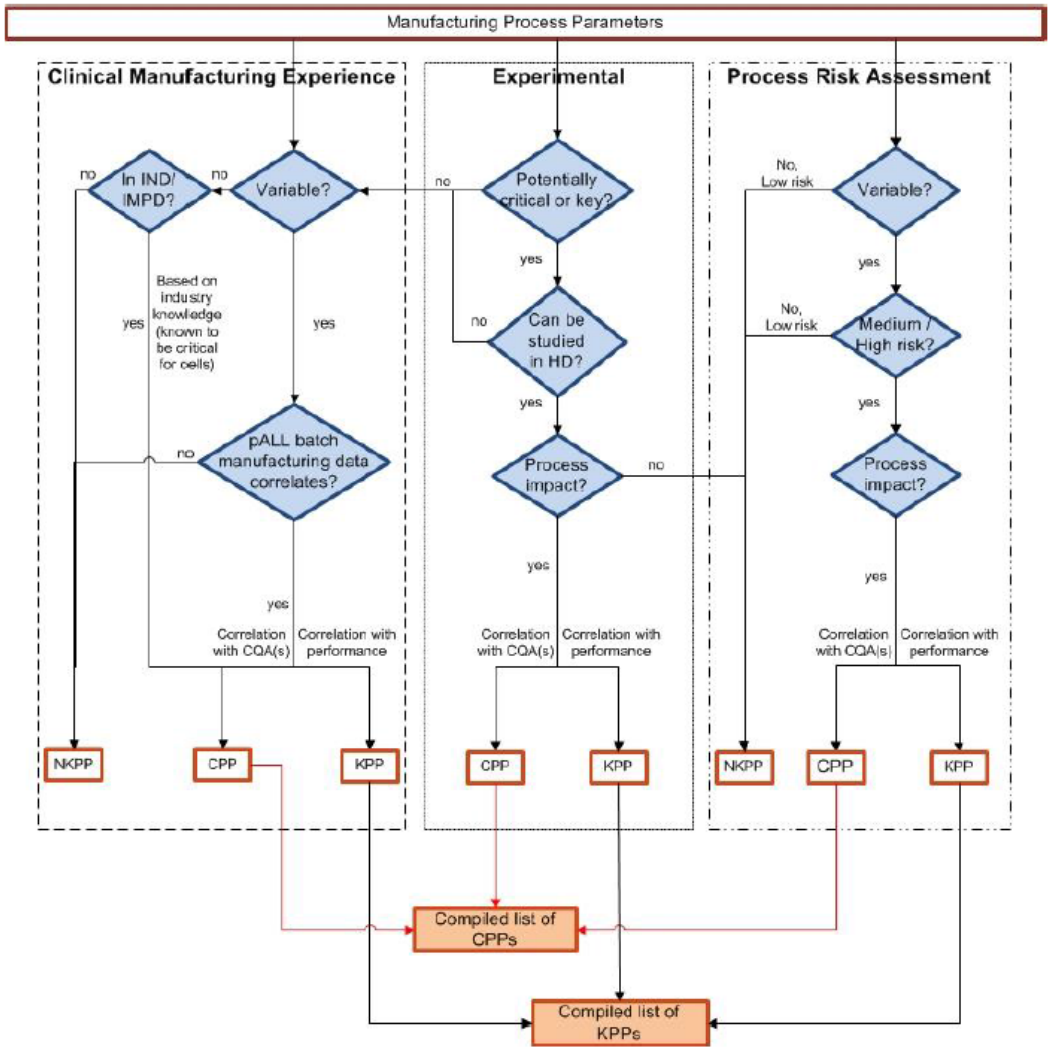
Process Characterization Approach

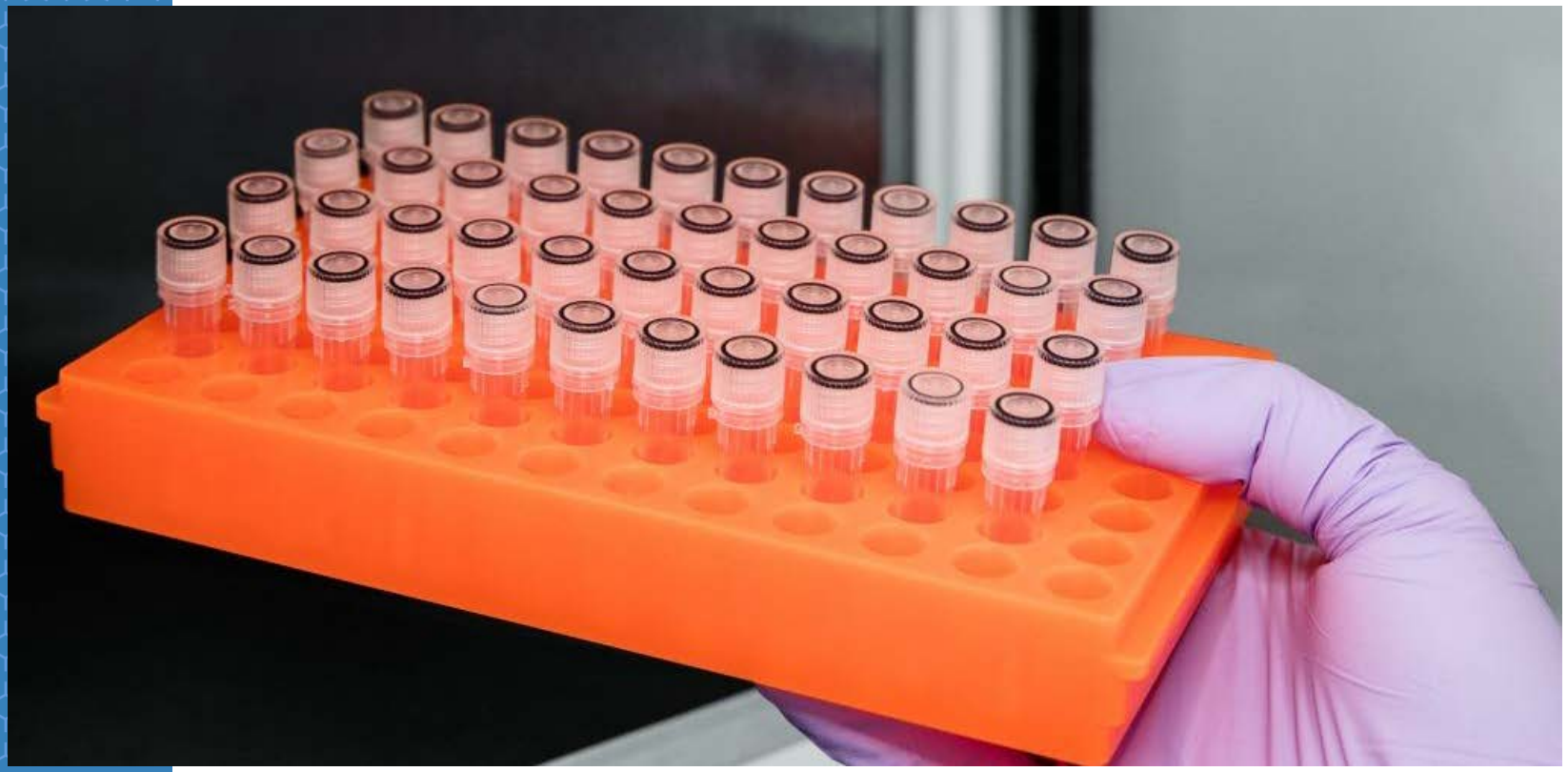






PC Implementation





Process Validation and Launch

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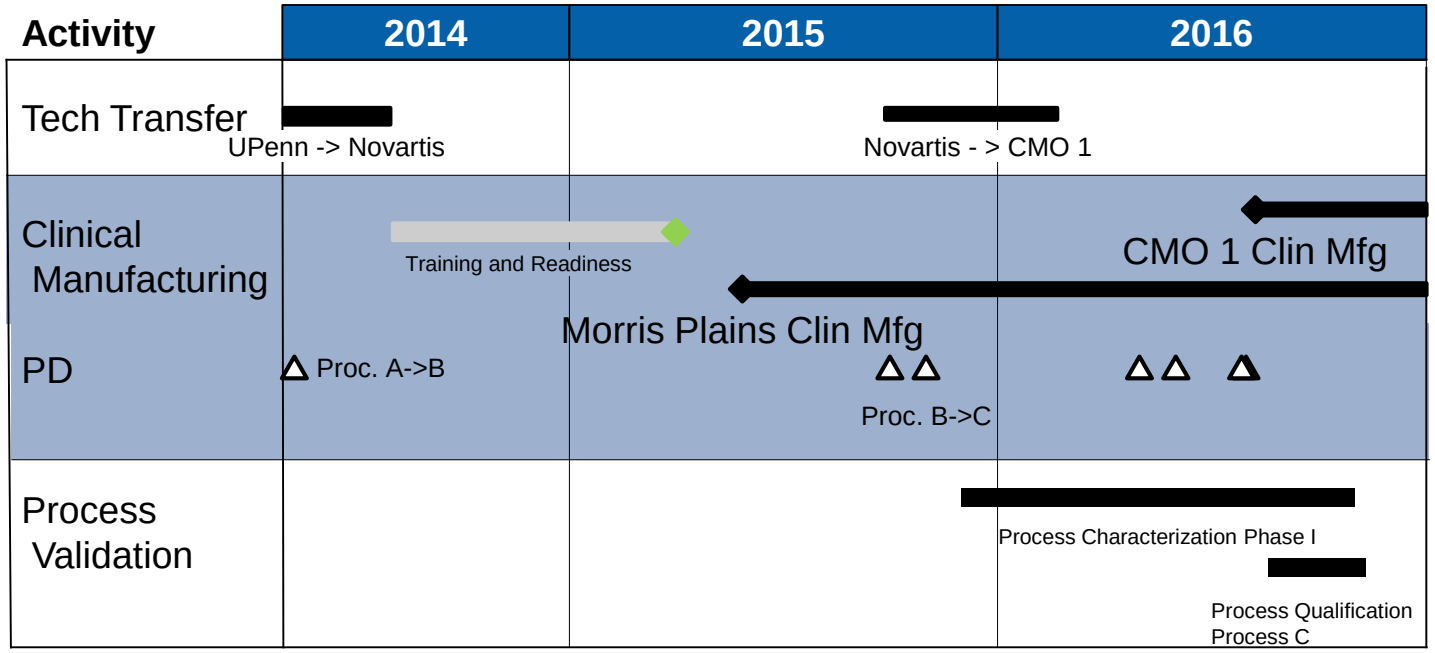
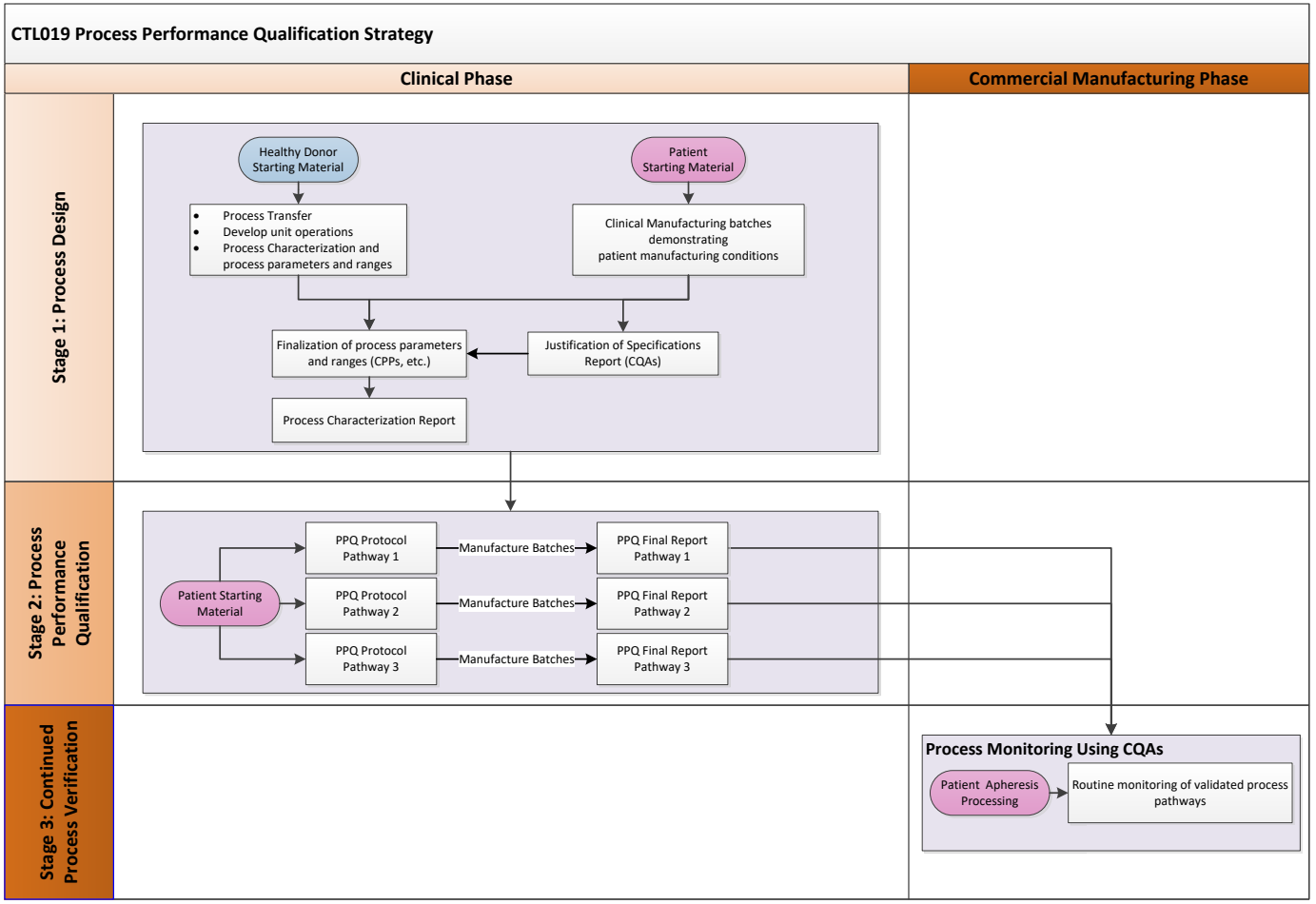
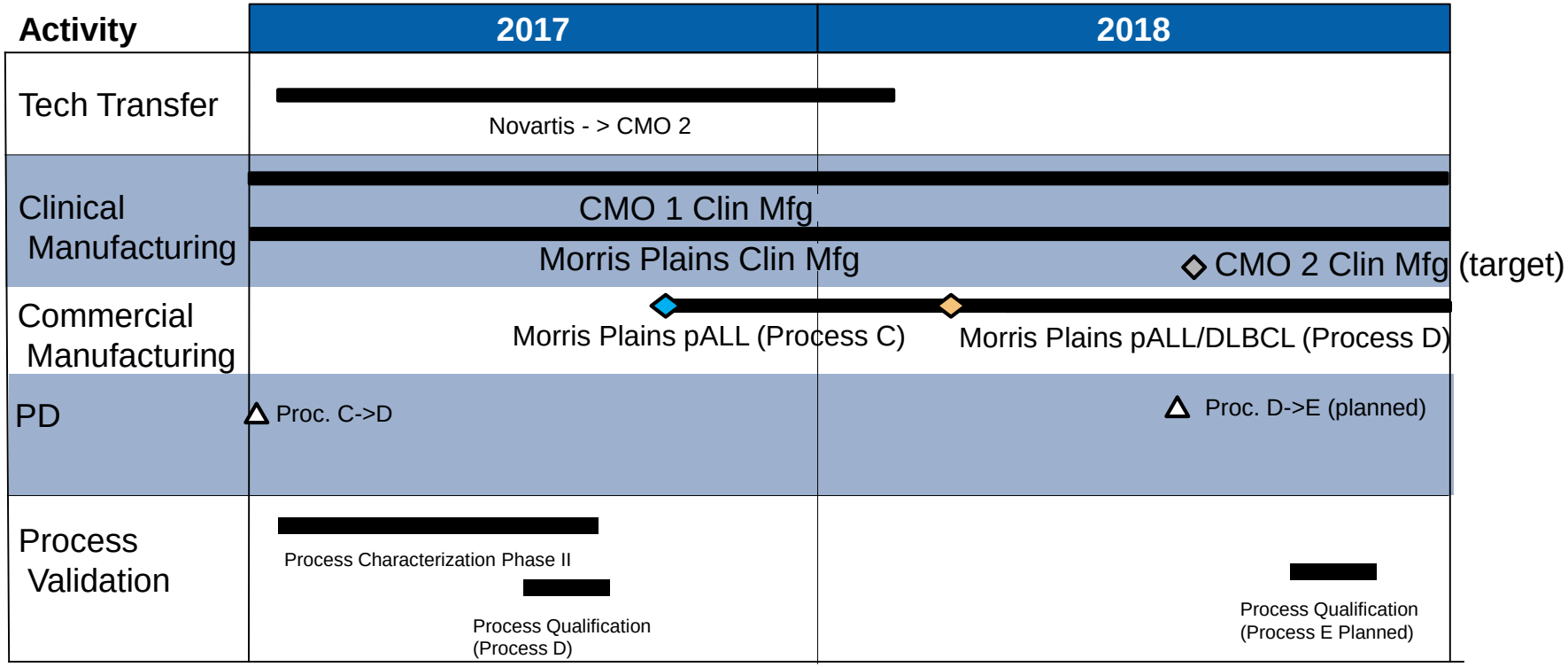
Initial Development Thru Qualification



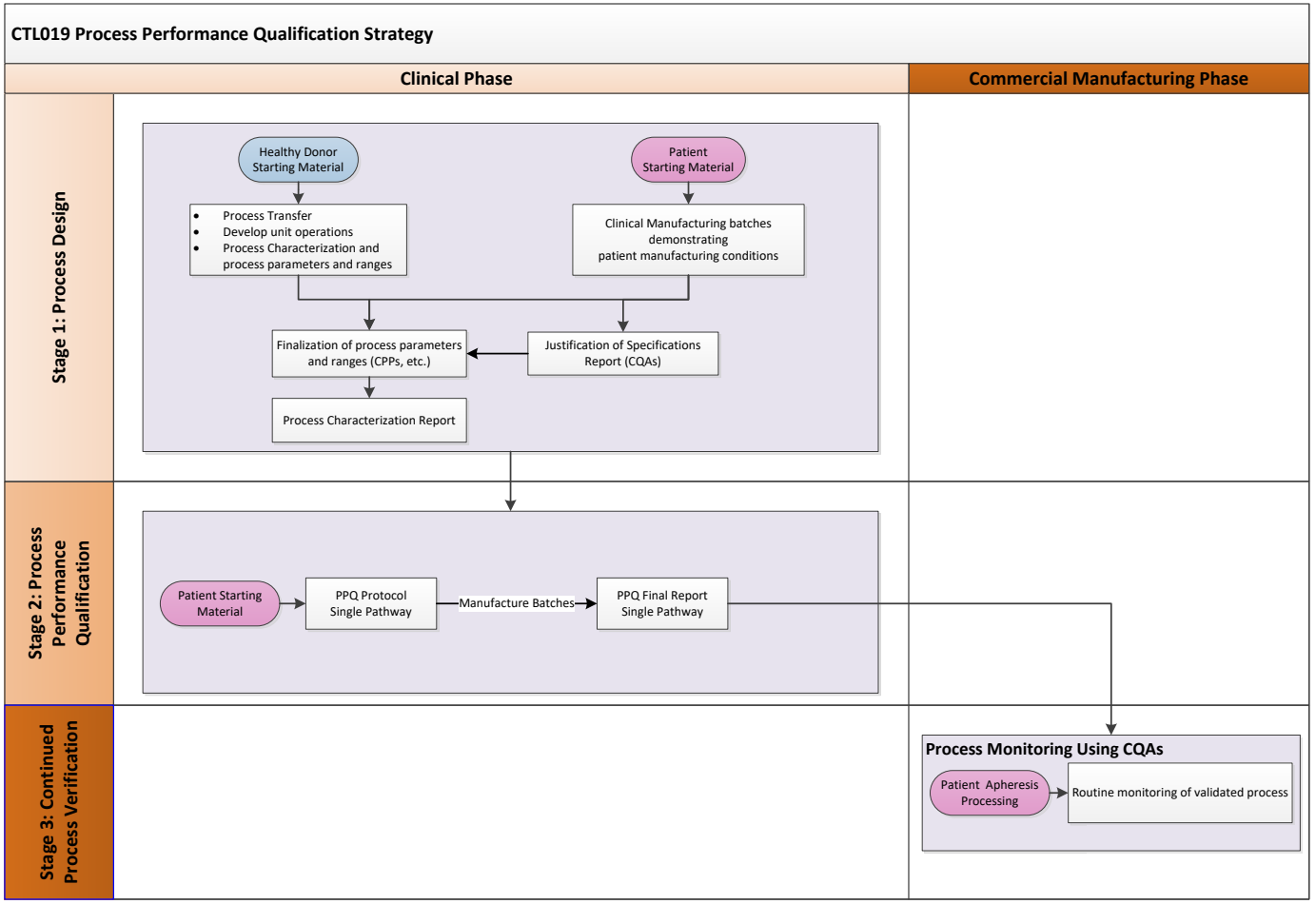
Initial Process Validation Approach



Continued Development and Launch



Current Process Validation Approach



Challenges / Lessons Learned

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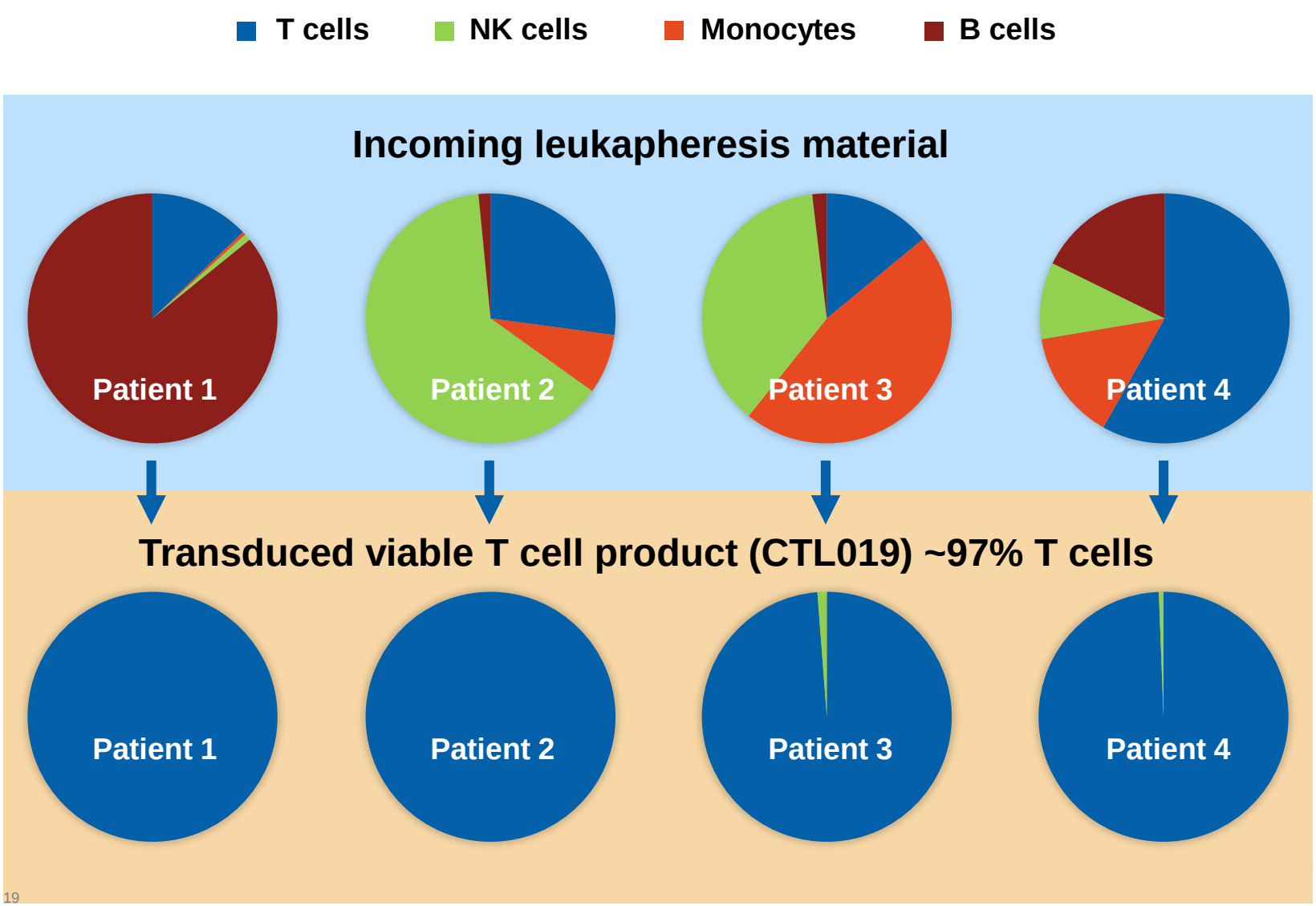
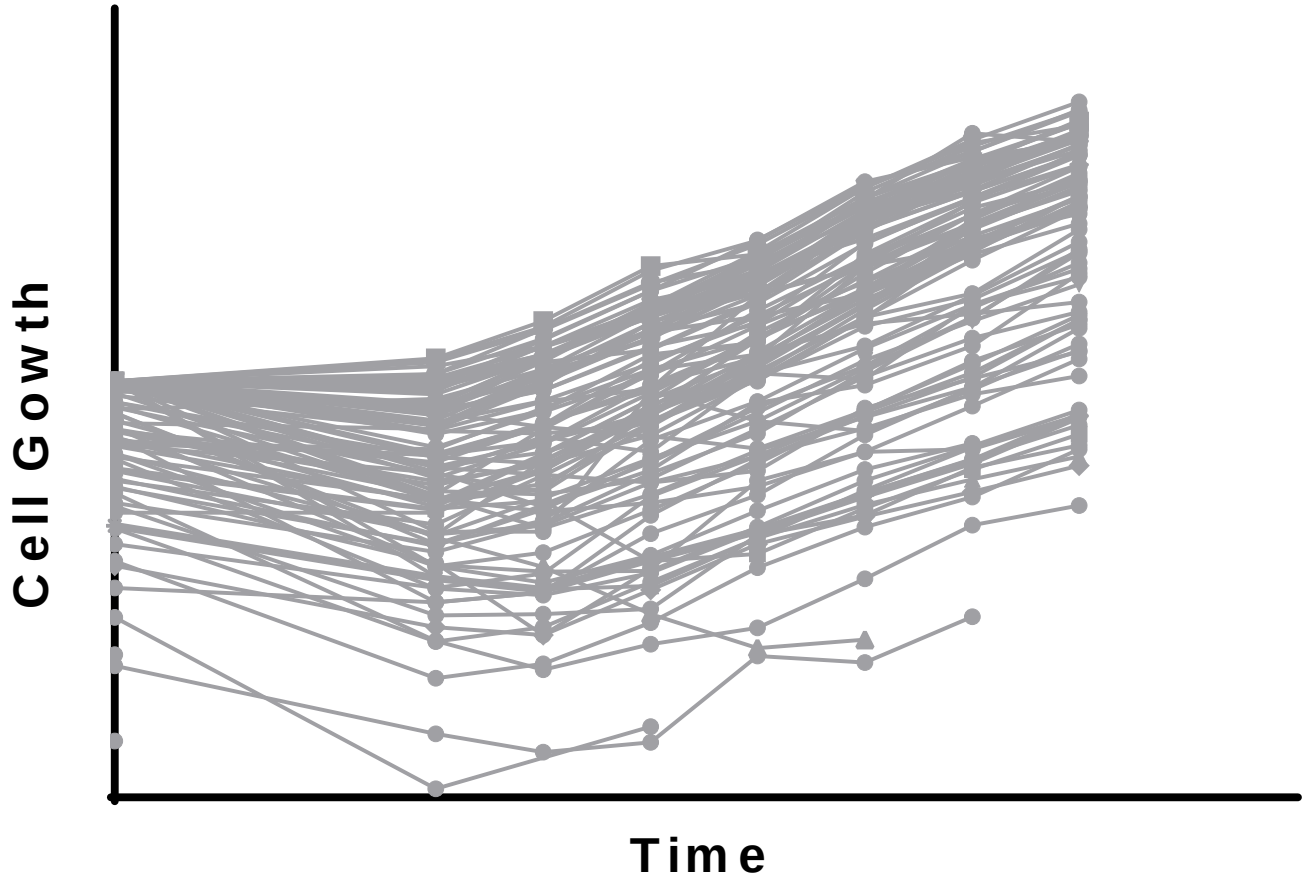
Consistent CTL019 T-cell product from individual patient material



Continual Learnings on Cell Growth



The Next Chapter of Kymriah™

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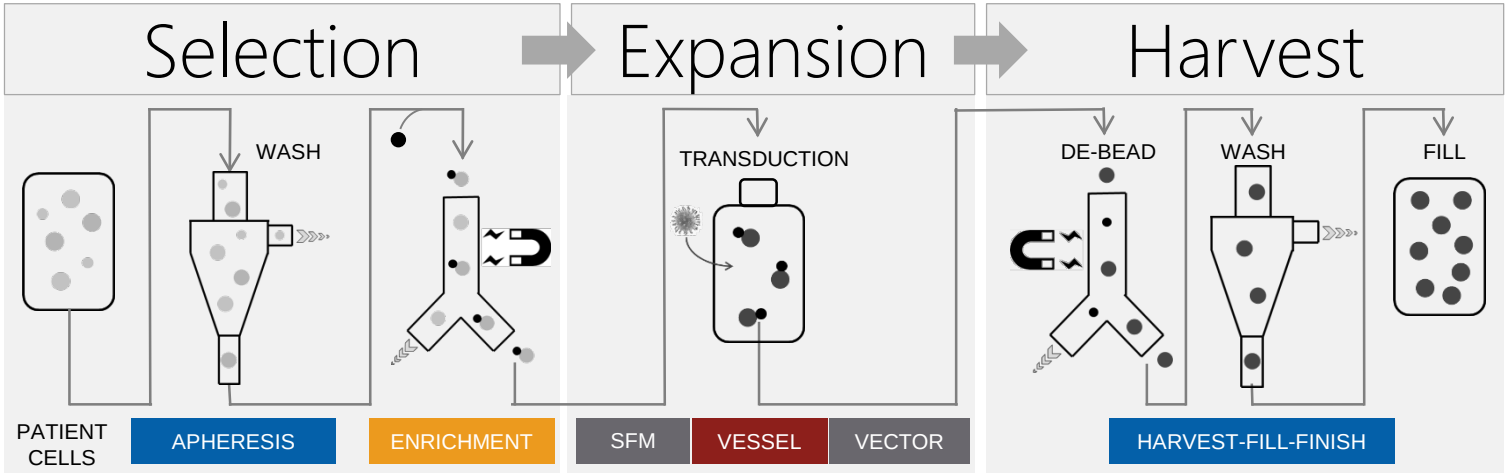
Near Term Process Improvements

- Additional steps moved from luer to tube weld connections
- More pre-assembled components
- Earlier introduction of cells to the WBR
- More robust cell selection
- Move to automation, particularly around de-beading, harvest and formulation
- Switch to vector produced via more robust/scalable methods
- Additions of secondary sources for key raw materials

Next Gen Manufacturing

- Automated, closed system, minimized footprint



Manufacturing Devices (6) → Manufacturing Devices (4)

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Thank you

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