A Case Study: Multiple process improvements implemented during clinical development …

Avid Bioservices®
Commercial and Clinical Biomanufacturing

… resulting in 10X production yield with consistent product characteristics

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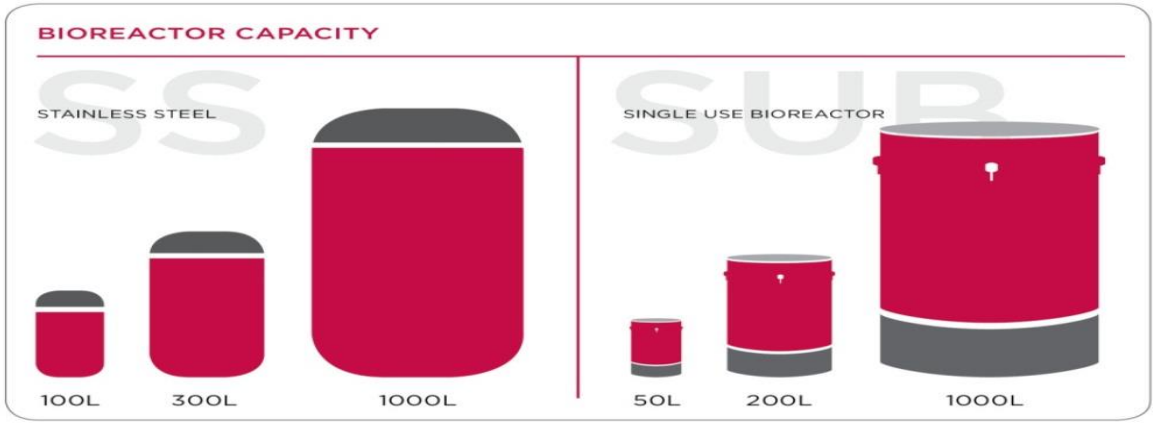
Avid Bioservices Company Overview

- CMO business established in 2002
- Significant experience in mammalian cGMP production
  - Hundreds of cGMP lots produced to date
  - Commercial production since 2005
  - >18 successful FDA and European inspections including multiple PAIs
- Innovative approach to manufacturing
  - Stainless Steel Bioreactor (SSB) production since 1997
  - Single Use Bioreactor (SUB) production since 2008
    - ❖ 1st CMO on west coast to implement SUB
  - Implementing disposable components in upstream and downstream processes



Today's Case Study

Outline

- Multiple process changes during clinical development
  - Scale-up
  - Change of cell line + downstream optimization
  - Implement SUB for manufacturing process
  - Optimize media and feed

Continuous Process Improvement to Support Clinical Development

Phase I

- Adequate but low titer process
- Support small clinical studies

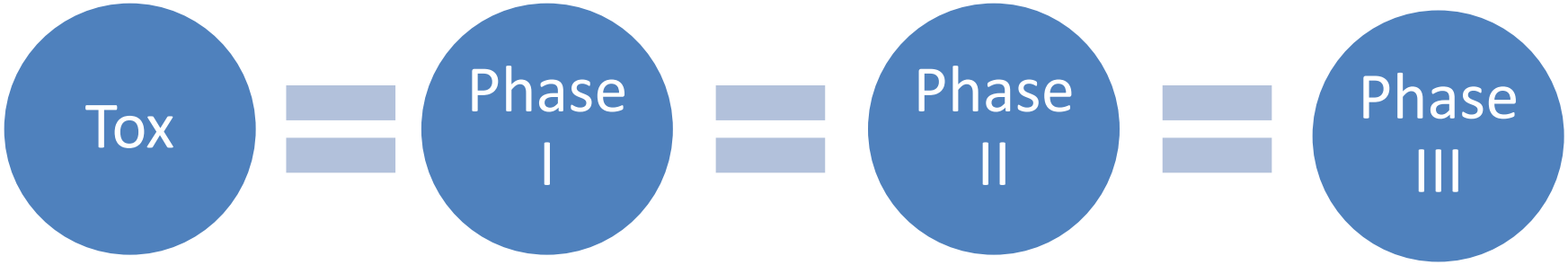
Phase II

- Higher Yields Needed
- Support mid sized clinical studies

Phase III

- High Yield Optimized Process
- Support Phase III and commercialization

Regulatory Strategy: Maintain High Degree of Product Similarity When Implementing Any Process Changes



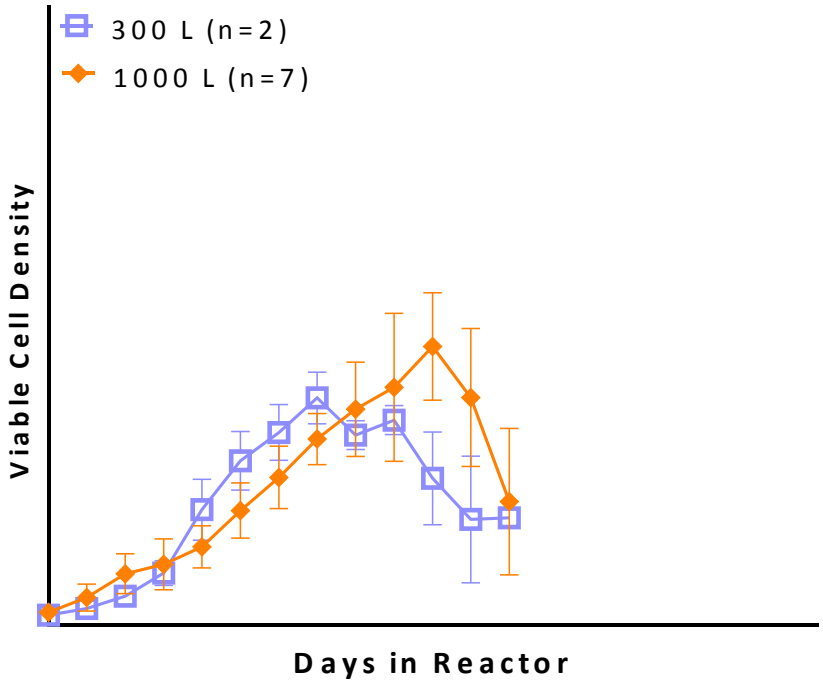
- Maintain Continuity of Clinical Data
  - Similar product throughout clinical development strengthens the package
- Eliminate need for human bridging studies or need to repeat toxicology studies
- Our approach is based on strong characterization package
  - Analytical Characterization
  - Small animal PK
- Our philosophy is NO manufacturing changes during Phase III and minimal modifications to support commercialization

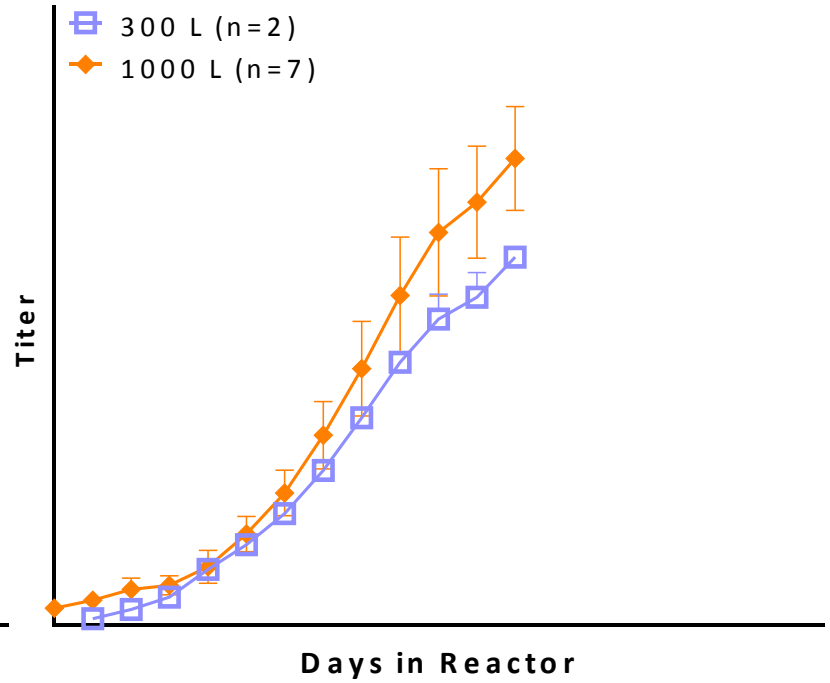
Phase I / Early Phase II Clinical Production

Process Scale-Up During Phase I and Early Phase II

- 1st generation process
  - 300 L Stainless Steel Bioreactor with a fed batch process
  - Animal component free media
  - One 300 L Stainless Steel Bioreactor yielded 150 clinical doses
- Process Scale-up
  - 300 L Stainless Steel Bioreactor to 1,000 L Stainless Steel Bioreactor
  - Supported Phase II clinical studies

Comparison of 300 L vs. 1,000 L Production





- Achieved similar growth and titer between two different scale productions

Degree of Similarity Analysis: 300 L to 1,000 L Scale-up

- Phase-appropriate analytical testing assessed comparability between the 300 L and 1,000 L drug substance

Lot Release and Characterization Assays	
Antigen Binding	Oligosaccharide Analysis
Monomer Content	Peptide Map
IEF	N-terminal Sequencing
SDS-PAGE	Stability

- Reports submitted to the FDA demonstrated a high degree of similarity between 300 L and 1,000 L Stainless Steel Bioreactor scales
- Process scale up resulted in the 1st generation process at 1,000 L scale producing **3X more** clinical material to support early Phase II

Phase II Clinical Production

Increasing Clinical Needs Necessitated Process Changes

- Phase II clinical trials require 1,000+ doses
- Cost of goods becoming another key consideration
- Later stage clinical studies may require thousands of doses

A number of process changes were implemented to address these needs and to improve manufacturing flexibility

- New cell line with greater potential for producing higher titer
- Downstream process improvements to improve purity profile
- Implement the use of 1,000 L SUB to give production flexibility through ability to produce in either Stainless Steel Bioreactors or SUB

2nd Generation Changes Designed to Increase Yield

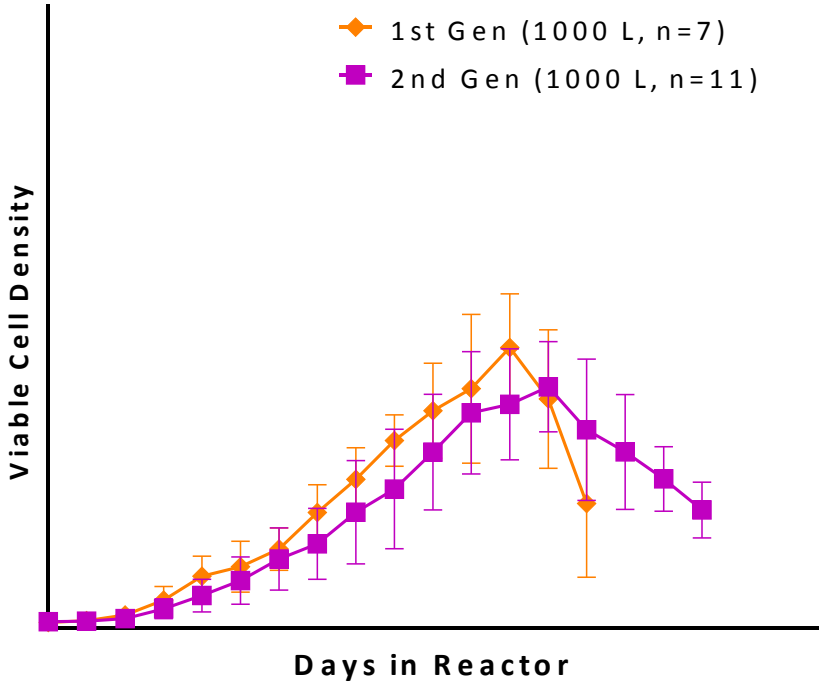
Cell Line and Process Changes:

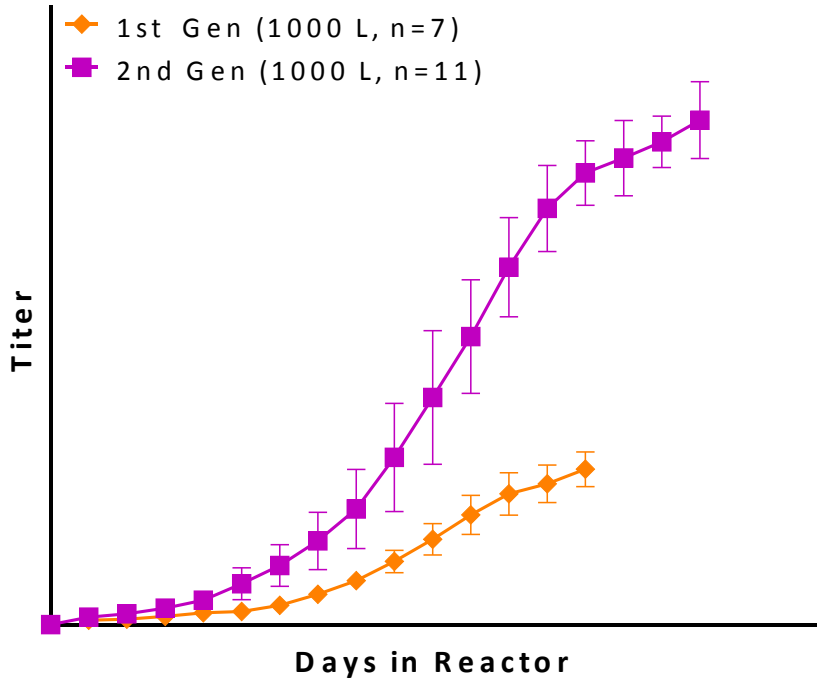
- New transfection and subcloning created a new cell line (2nd generation cell line)
  - ~3X more product than the 1st generation process
  - Animal component free fed batch
  - Produced in 1,000 L Stainless Steel Bioreactor
- In addition, modernized downstream process to increase product purity

Implementing SUB into manufacturing process:

- Established production in 1,000 L SUB

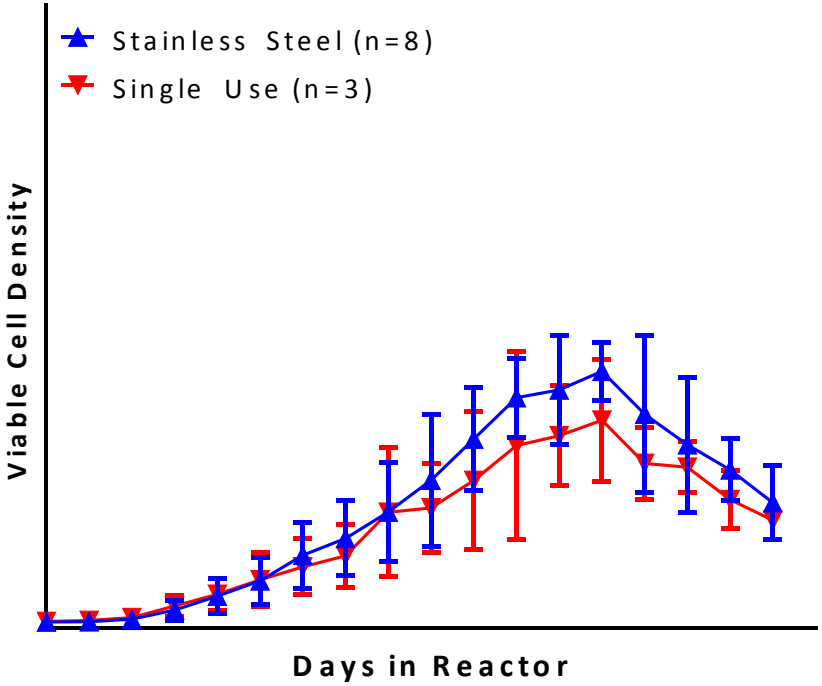
Comparison of 1st and 2nd Generation Cell Lines

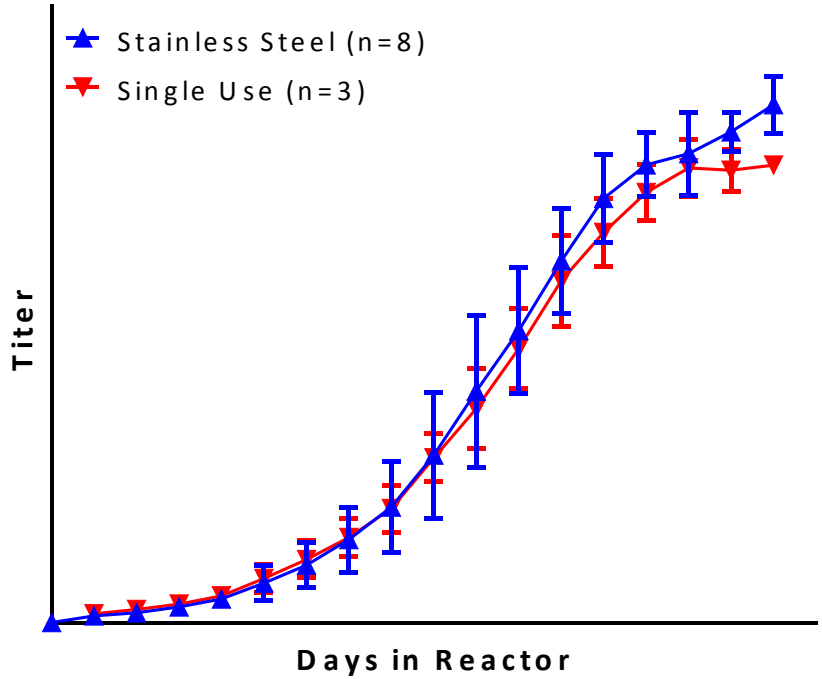




- Similar cell growth
- 2nd generation cell line produced **~3X** higher titer

Comparison of 1,000 L Stainless Steel Bioreactor and 1,000 L SUB





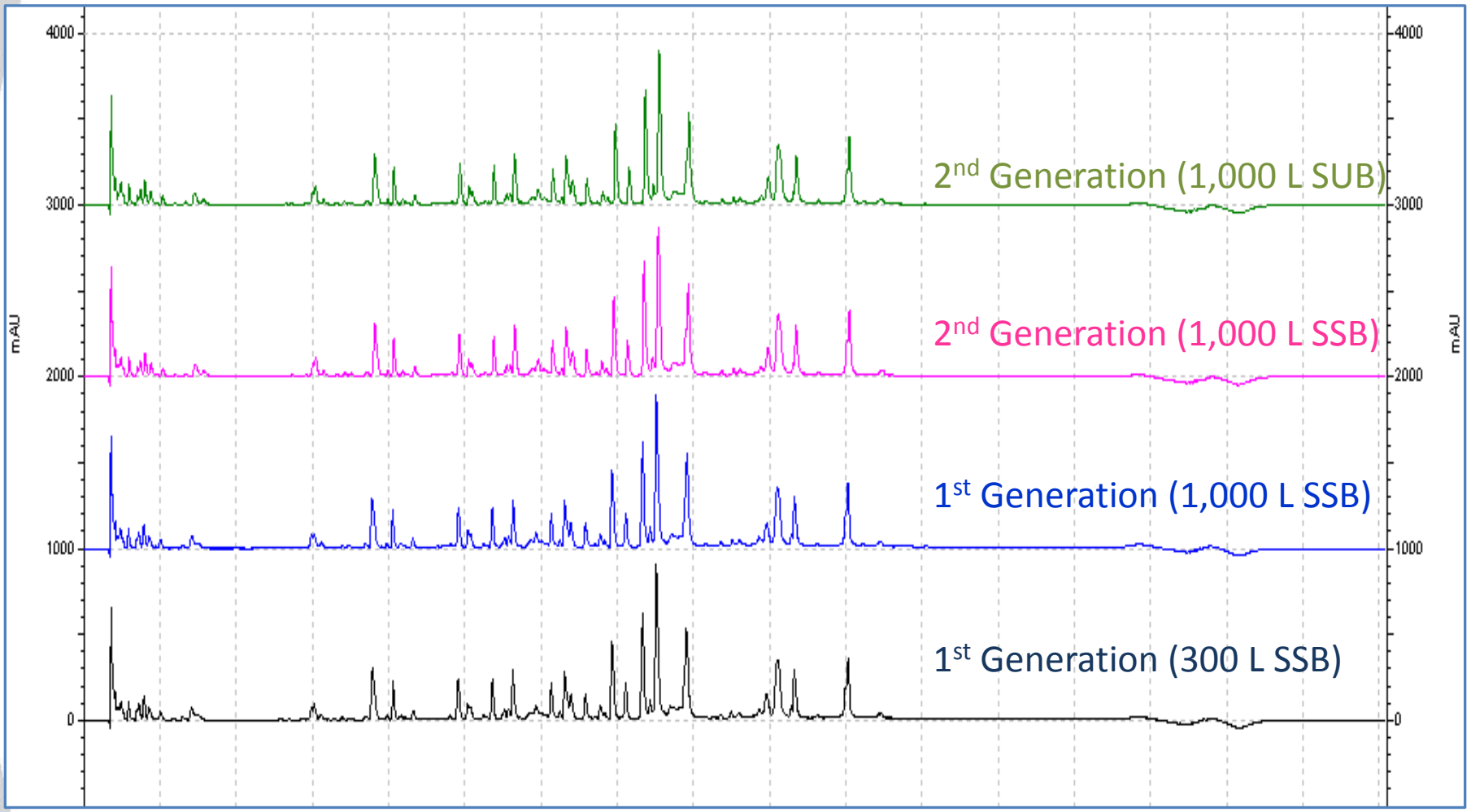
- Comparable upstream process
- Similar cell growth and titer between Stainless Steel Bioreactor and SUB

Product Comparability Analysis to Support 2nd Generation Production Process Changes

- Degree of similarity was demonstrated with lot release, analytical characterization and stability data

Lot Release for Drug Substance/Drug Product		Additional Characterization
General	Identity	Analytical Ultracentrifugation
Visual inspection	IEF/cIEF	N-terminal Sequencing
Color and Appearance	Peptide Map	C-termincal Sequencing
Particulate Matter (DP)		Monosaccharide Composition
pH		Neutral Sugar Assay
Strength and Potency	Process-Related Impurities (DS)	Stability Studies
Protein Content	Residual Protein A	
Antigen Binding	Residual DNA	Non-Clinical Pharmacokinetics in Small Animal Model
Potency Bioassay	HCPs	
Safety	Purity	
Endotoxin	SEC	
Bioburden	IEX	
	SDS-PAGE	
	Oligosaccharide Analysis (DS)	

Example of Comparable Product Characteristics Assessed by Peptide Map



Tox = Phase I = Phase II

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Summary of Changes Made During Phase II

- Process changes made during Phase II resulted in a product which met BOTH analytical and animal PK bioequivalence criteria.
- Package submitted to FDA resulting in approval for:
  - Process changes
    - Cell line
    - Optimized downstream process
  - Interchangeable production in Stainless Steel Bioreactors and SUB

Phase III Clinical Production

Process Changes Made in Preparation for Phase III
2nd Generation Cell Line w/ Optimized Media and Feed Strategy

One single Phase III clinical trial requires ~5,000 doses (estimate)

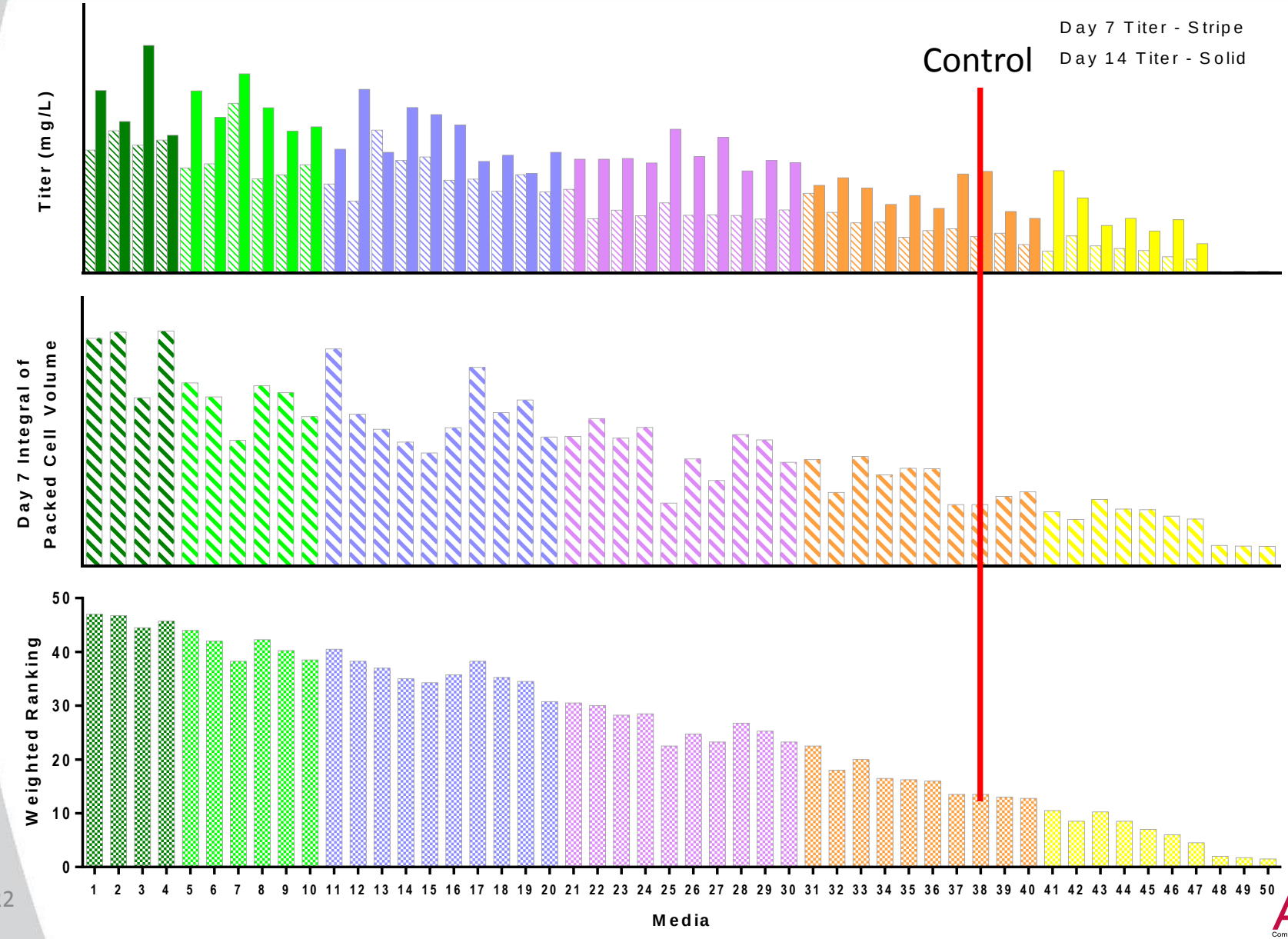
- To support Phase III and commercialization, the 2nd generation cell line was further optimized for higher yield
- Process optimization involved
  - New media selection
  - New feed strategy
  - Optimized bioreactor conditions
- Completely disposable inoculum
- Produced in 1,000 L SUB

➢ How did we achieve this?

First Step: HTP Media Screening

- Screened 50 different media in duplicate
- Checked Packed Cell Density (PCD; Day 0, 5, 7, and 10)
- Checked titer on Day 7 and 14
  - Protein A titer analysis by HPLC
- Created a ranking system based on PCD and titer
- Chose 3 media to move forward
  - Adaptation and larger growth studies in spinners
  - Test product characteristics
  - Selected 2 media for feed screen studies

1st Step: Media Screen



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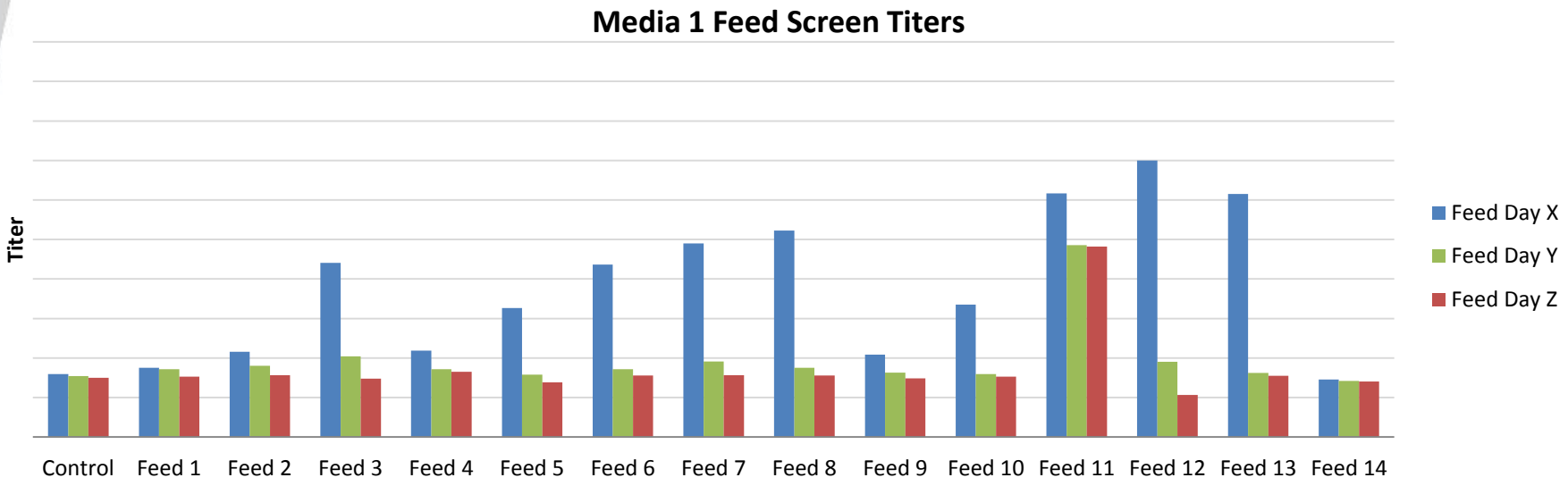
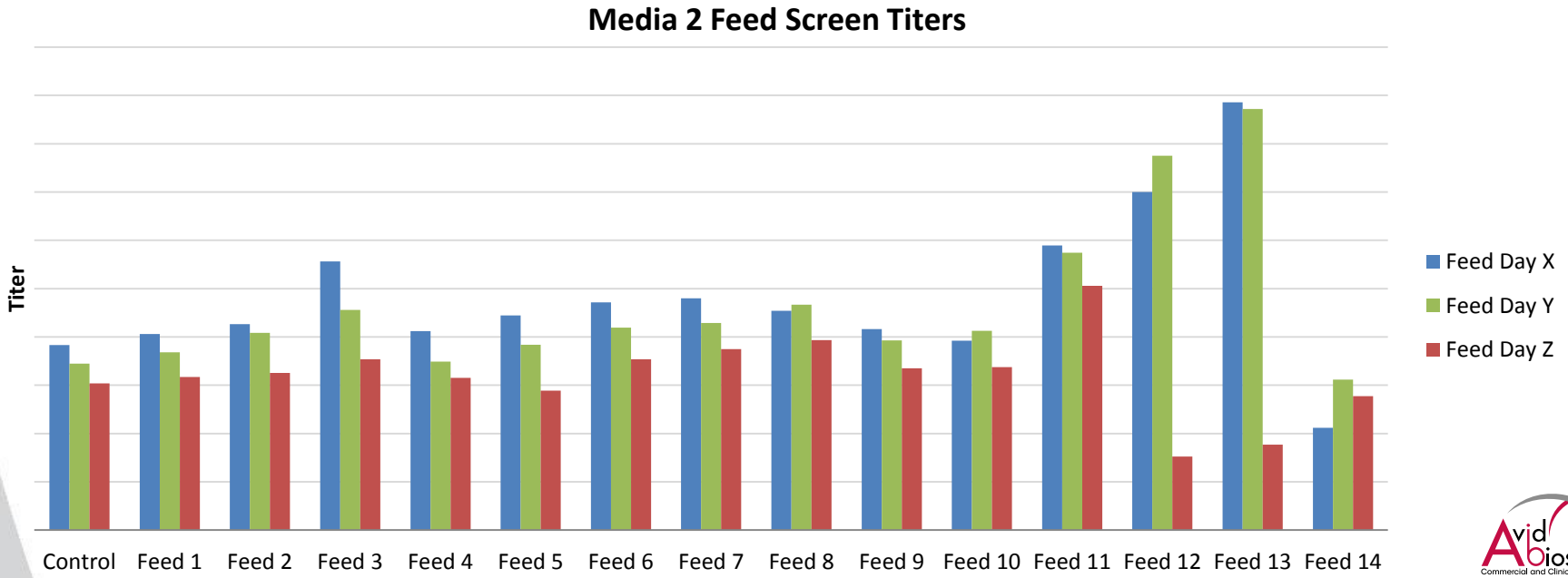
2nd Step: Feed Screen



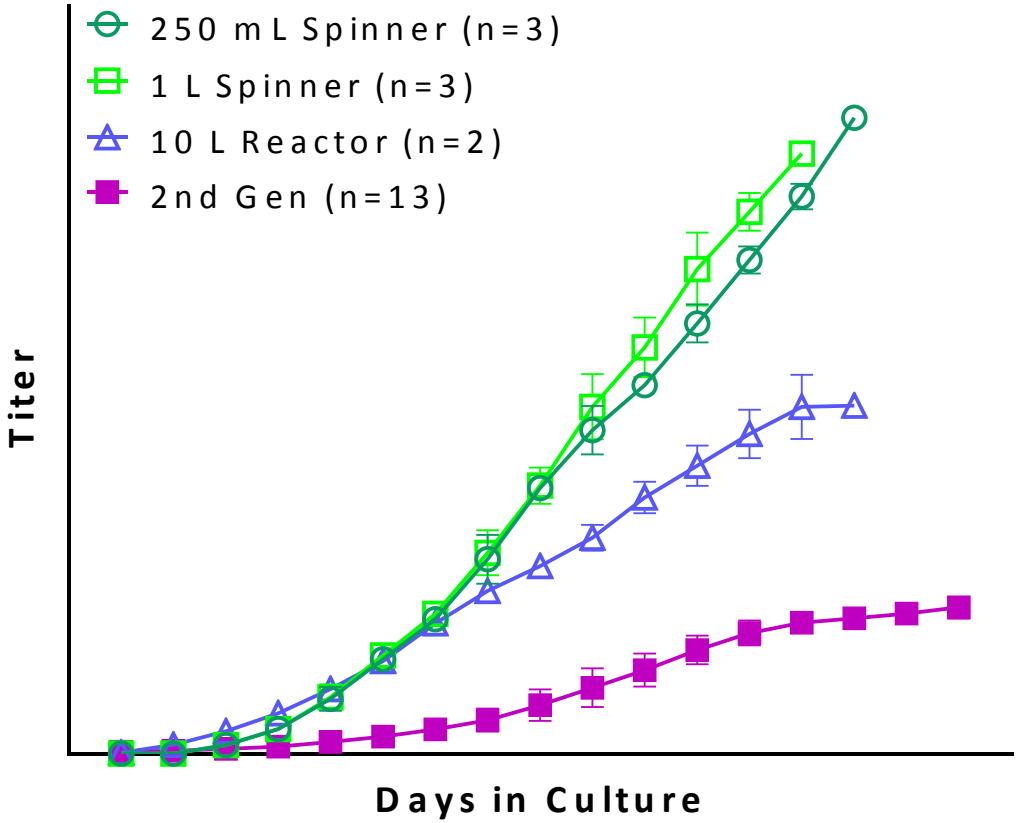


2nd Step: Characterization of Feed Screens

- Purified product from highest producing conditions
- Assays performed
  - Antigen Binding
  - Cation Exchange Chromatography
  - Size Exclusion Chromatography
  - Carbohydrate analysis
- Reduced to only 1 medium and tested combinations of the most effective feeds

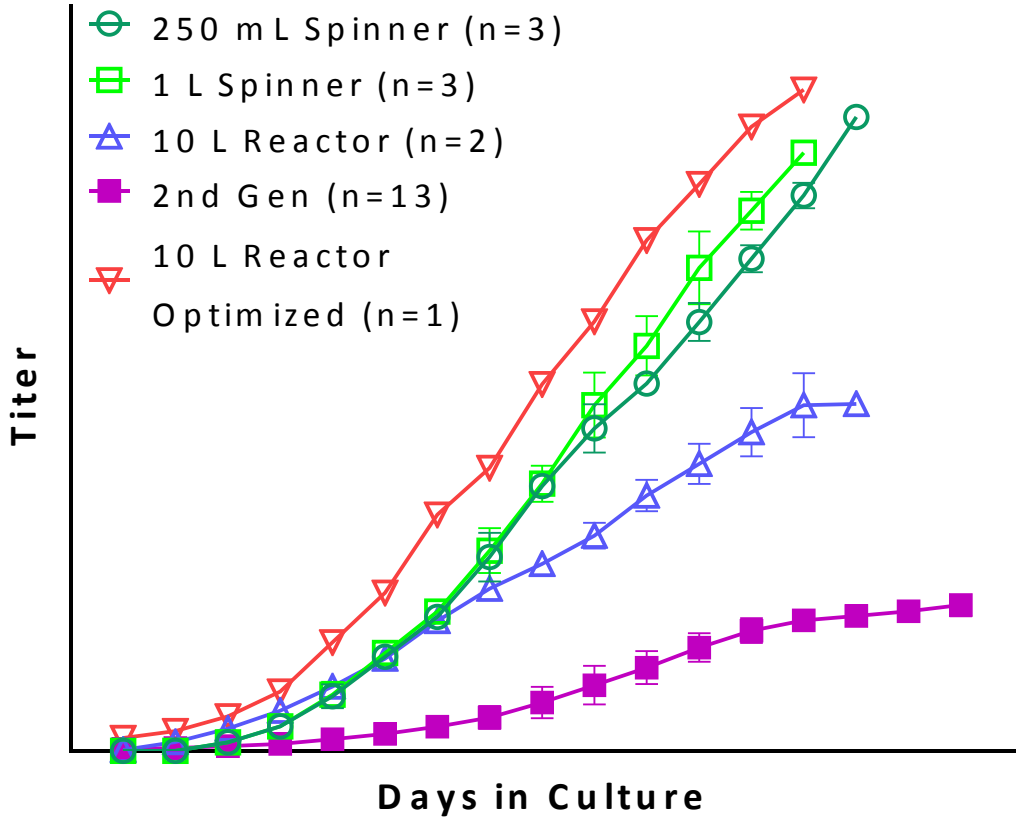
3rd Step: Combination Feeds/Multiple Days

- High Throughput Screening of multiple feeds over multiple days achieved our goal of a 4X increase in titer
- Moved on to small scale spinners followed by reactor trials

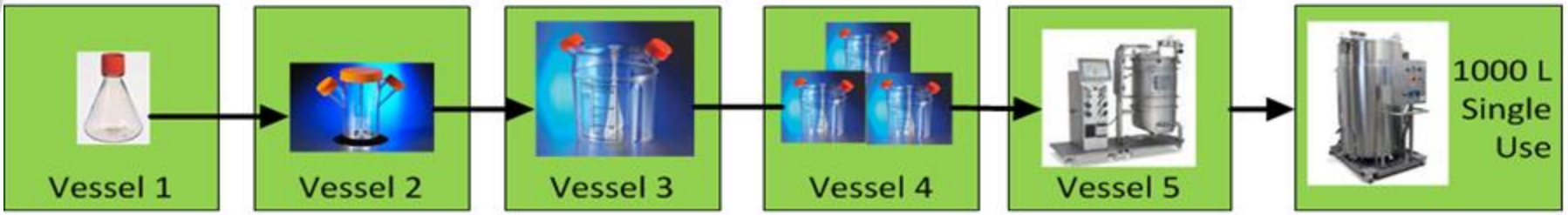


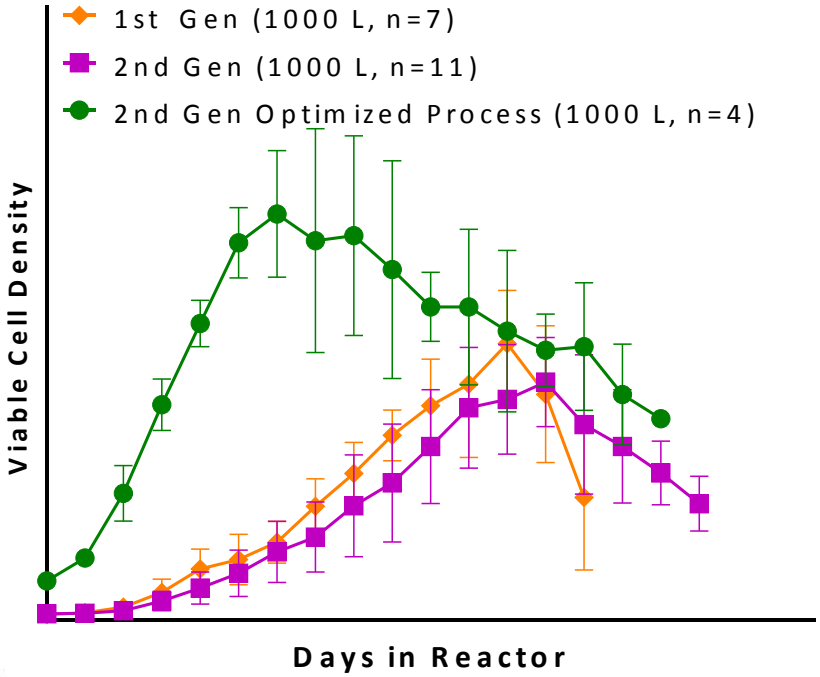
4th Step: Reactor Condition Optimization

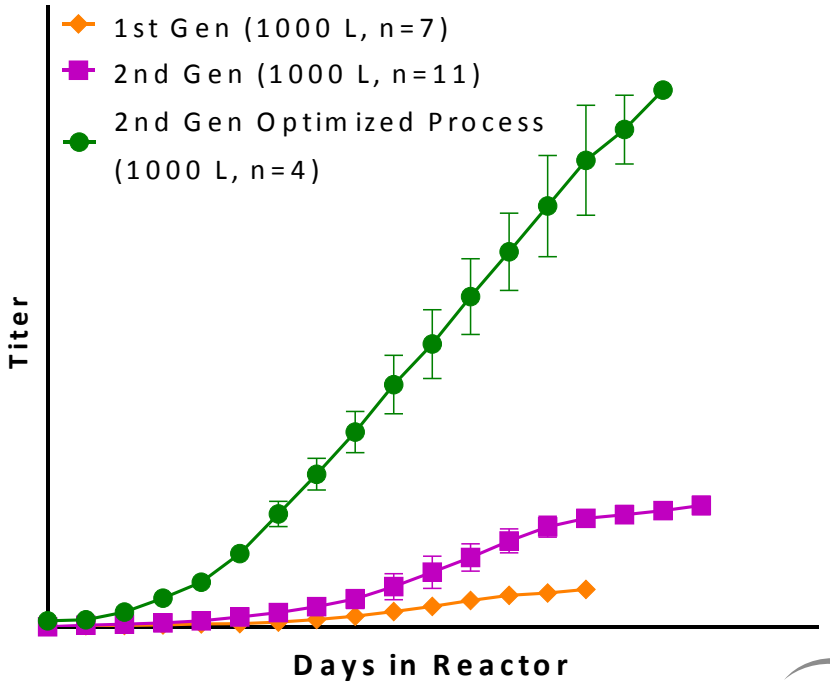
- Inoculum density was evaluated
- Sparging strategy was evaluated
- Timing of the feeds were evaluated



2nd Generation Optimized Process Performance







Product Comparability Demonstrated

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General	Identity	Analytical Ultracentrifugation
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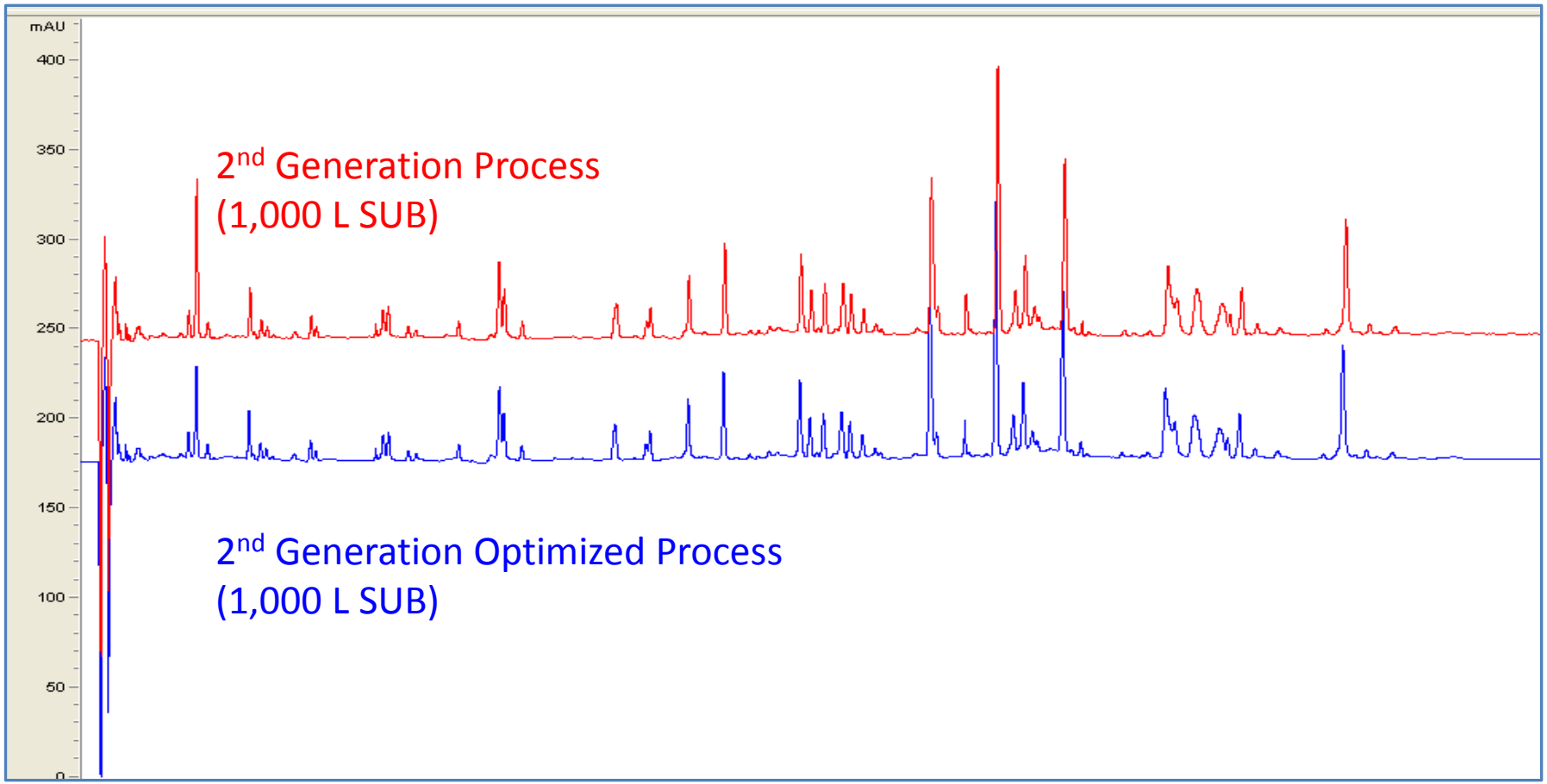
Safety	Purity	
Endotoxin	SEC	
Bioburden	IEX	
	SDS-PAGE	
	SDS-CGE	
	Oligosaccharide Analysis (DS)	

2nd Generation Product Comparability Peptide Map



Summary: Changes Made for Phase III Clinical Trials

- Process changes (new media, new feed strategy with optimized bioreactor conditions and completely disposable upstream process)
  - Resulted in **more than 4X increase** in production with a high degree of similarity in product quality attributes

- Complete data package submitted to FDA as an IND Amendment resulting in approval for these process changes

Summary: Multiple Process Changes During Clinical Development

Phase I

- 1st generation cell line, limited process development (300 L SSB)
- One 300 L batch resulted in ~150 clinical doses

Phase II

- Scaled up from 300 L to 1,000 L SSB (~500 doses)
- 2nd generation cell line with optimized downstream process
- Then 1,000 L SSB to 1,000 L SUB
- 3X increase in titer resulted in 1500+ clinical doses

Phase III

- 2nd generation cell line, optimized feed strategy (1,000 L SUB)
- > 4X increase in titer over 2nd Gen resulted in ~ 7000 clinical doses

➢ Product Comparability was demonstrated through analytical characterization package and small animal PK

Acknowledgement

- Our client and their regulatory group
- Robert Garnick
- ExcellGene
- Avid Process Sciences
- Avid Manufacturing
- Avid QC/QA
- Accounting (paying the bills)

Thank You!

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