PlenShop Comparability Example:
Late Stage Implementation of Major Process Changes

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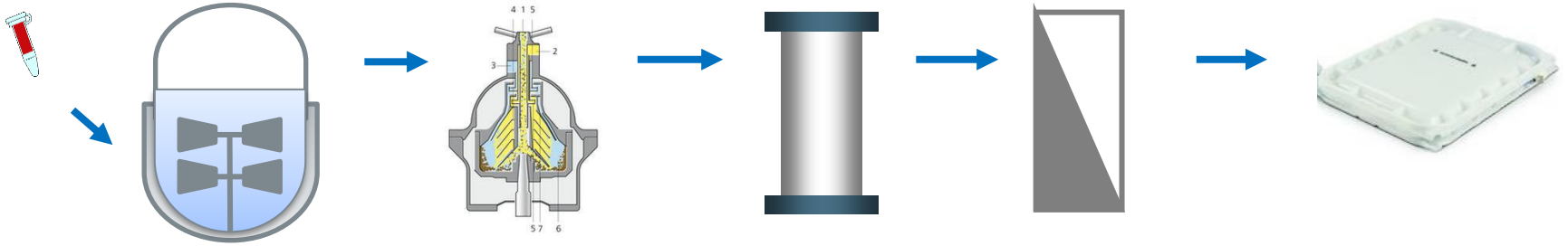
Situation and Driver for Process Changes

- IgG1 monoclonal antibody
- Neurology indication
- Intravenous administration

- Ph3 clinical trials (~20 countries) used the previous DS/DP process and formulation
- Clinical program skipped Ph2 studies, so no time to develop commercial process prior to Ph3

- More productive process required to support anticipated commercial demand
- Accelerated clinical timelines → pressure to achieve product quality that enables comparability through analytical testing

Productivity Improvements Implemented to Meet Anticipated Demand



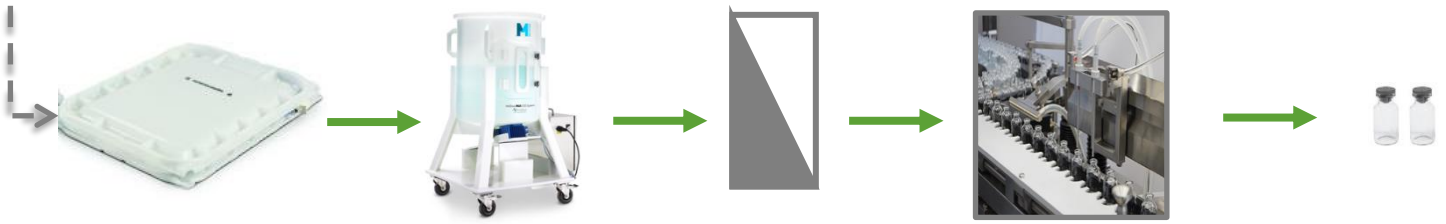
Inoculum Train & Production Bioreactor

Harvest / Clarification

Purification

Filtration & Concentration

Drug Substance
Frozen in bags

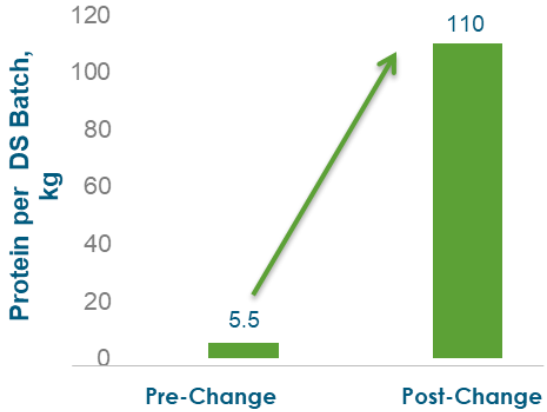


Thaw Drug Substance

Filtration

Filling & Capping

Drug Product
Liquid in glass vials



Productivity Improvements Implemented to Meet Anticipated Demand

- Cell bank further amplified
- Bioreactor scale increased from 2000K to 15000L
- Cell culture process optimized for productivity while maintaining product quality

Modifications to purification process made to accommodate increased protein mass coming from bioreactor and increase facility throughput

DS/DP Formulation buffer optimized for product stability

Harvest / Clarification

Purification

Filtration & Concentration

Drug Substance
Frozen in bags

Commercial drug product manufacturing sites accommodate larger batch sizes

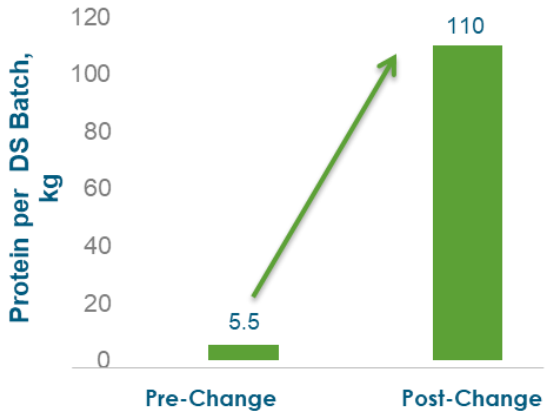
DP concentration increased; Vial size and fill volumes optimized for commercial presentations

Thaw Drug Substance

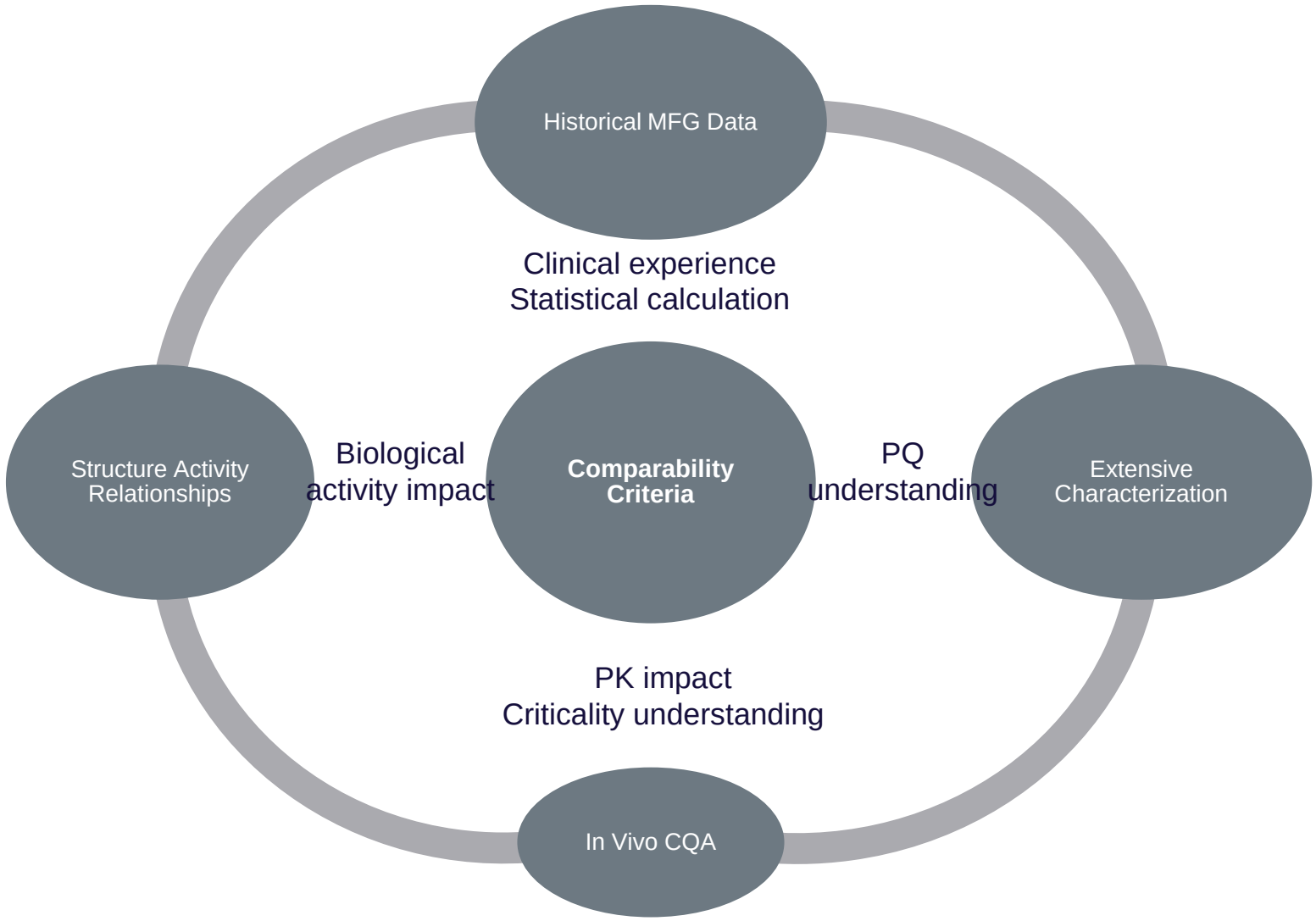
Filtration

Filling & Capping

Drug Product
Liquid in glass vials



Comparability Protocol Approach



Comparability Plan

- Comparability plan consistent with ICH Q5E principles, including pre-defined comparability criteria → increased predictability and transparency

Extensive Product Understanding

- Product understanding / SAR data used to justify comparability ranges

Regulatory Advice

- Seek advice from regulatory agencies → better understanding of expectations for comparability

Comparability Plan

Drug Substance	• **Release and Characterization attributes:** Post-change batches compared to historical results from prior process and reference standard • **Accelerated and stressed "forced deg" studies:** Pre- and post-change side-by-side (3 batches each) to determine if the post-change process material generates impurities not present in pre-change process material (qualitative assessment)
Drug Product	• **Release Testing:** Post-change batches compared to historical results from prior process and reference standard • **Comparison of degradation pathways:** Qualitative assessment of impurity species that develop during GMP DP stability; e.g, evaluate peaks in chromatograms / electropherograms compared to pre-change material
DS/DP GMP Stability	**Increase in DP protein concentration may impact the rate of aggregation; thus, expiry from the previous process may not be directly leveraged for new process.** • Determine appropriate expiry for new process material to ensure patients are exposed to comparable product

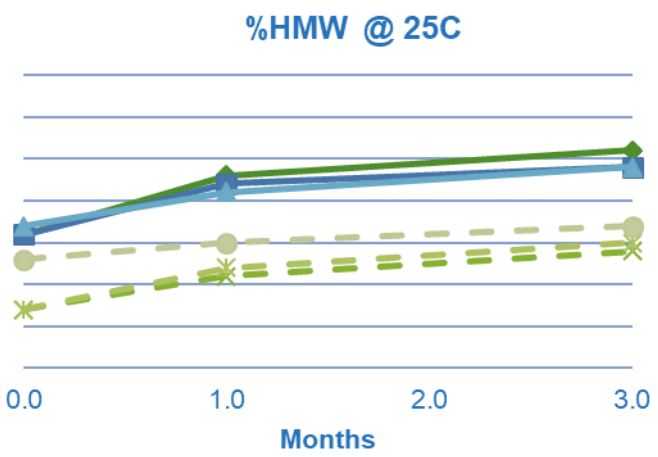
Comparability Study Results: Release and Characterization

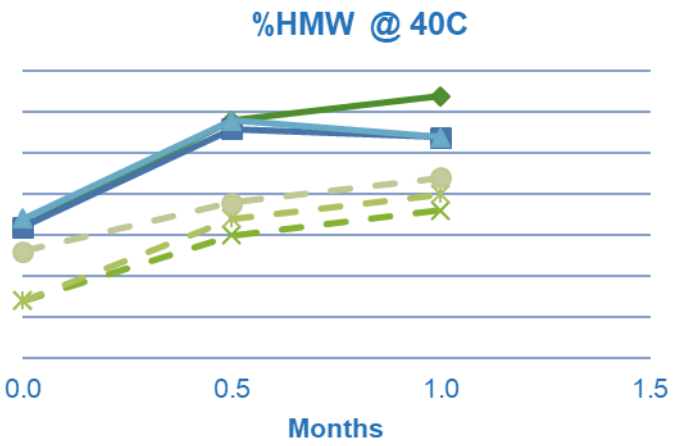
- All attributes (release and characterization) met pre-defined comparability criteria

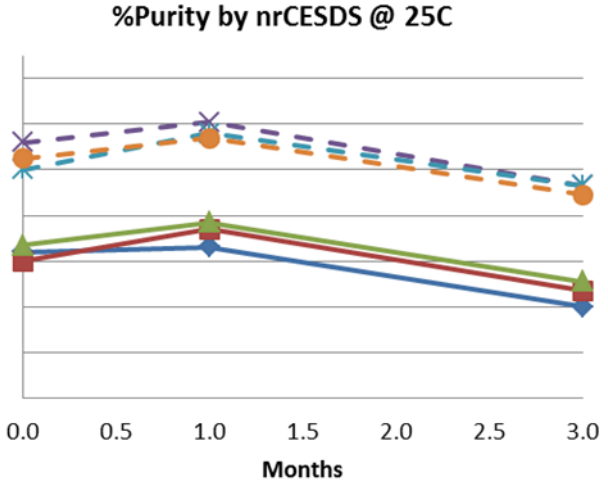
- The only critical quality attributes that fell outside of the historical manufacturing experience range are improved (lower %HMW by SEC and higher %Purity by CE-SDS in post-change DS and DP)

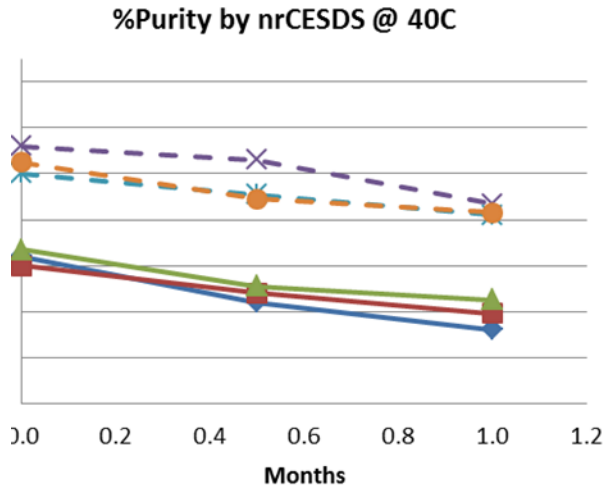
- No new species were observed in the post-change DS and DP

Forced Degradation Profiles of Pre- and Post- Change DS are Consistent







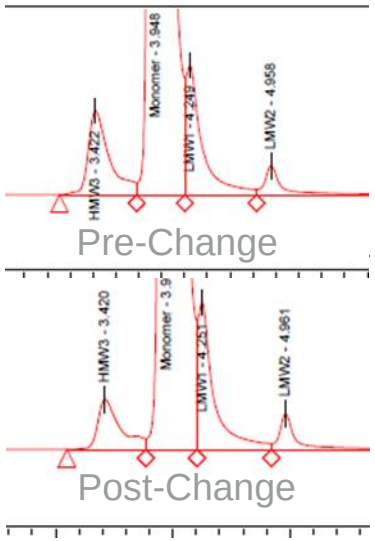


Pre-Change DS (solid lines)

Post-Change DS (dashed lines)

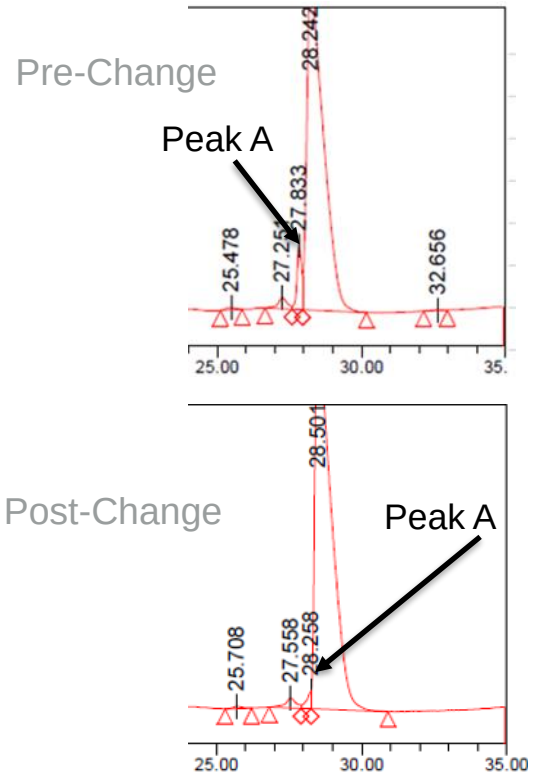
Forced Deg DS Samples Confirm No New Impurity Species Post-Change

SEC (1M 40°C)

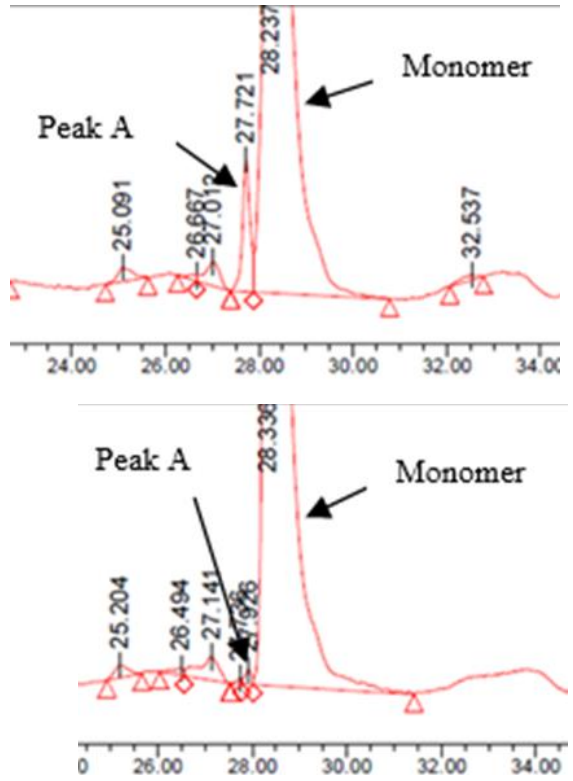


- Consistent profiles for Pre- and Post- change DS
- No species larger than dimer were observed in pre- and post- change DS (by AUC and SEC MALS)

NR CE-SDS (T0)



NR CE-SDS (3M 25°C)



- 2 peaks detected in Post-Change DS in area where Pre-Change DS only shows Peak A (extra peak in Pre-Change DS may be hidden under larger Peak A)
- Samples were tested by Reducing CE-SDS → showed comparable profiles for both processes, confirming no new impurity species

Outcome

- Clinical trial amendments filed in ~20 countries
- No queries received with respect to comparability
- Cleared to introduce new process material into ongoing Ph3 studies based on analytical comparability data
- New process material used in Ph3 extension studies
- Process validated to support commercial manufacturing
- Marketing application approved… Onto LCMs!

Discussion

- Significant work done even prior to manufacturing may be beneficial to reduce risk.
  - Extensive molecule characterization to increase product understanding
  - Seeking agency feedback
- Despite major process changes late in development, analytical comparability according to ICH Q5E guidelines was sufficient to support implementation in all markets as the results demonstrated no clinically meaningful impact.
- Telling the comparability story in the marketing application can be complicated
  - Multiple process and method changes over many years
  - Challenge is to organize and explain the information clearly so that reviewers can assess and come to their own conclusions
  - Some agencies may have specific preferences on how information is presented