Advances and Challenges with Tech Transfer, Scale-up, and Comparability

Cell Culture Engineering XVIII

April 24, 2023

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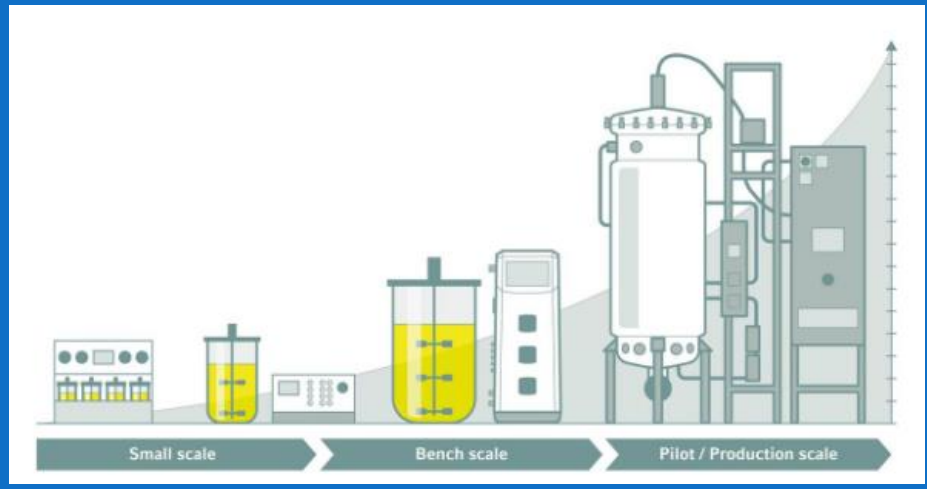
Catalent BIOLOGICS GSK Biogen



The content of this presentation and any discussions as part of this workshop are reflective of our own personal opinions and not those of our employers.

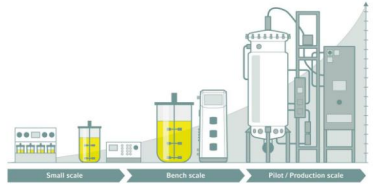
Introduction

Scale-up, tech transfer, and comparability have been long-standing important topics in the biopharmaceutical industry.

Despite the age of our industry, there are still challenges in scale-up occurring. We have advanced strategies over the years to increase scale-up and tech transfer success rates, but some surprises still arise and new modalities present unique challenges.

Additionally, compelling process drivers (e.g., product quality and increased productivity) have led to more significant late phase changes which require sound rationale and data sets to support a clear comparability strategy, often on accelerated timelines.

New technologies and approaches are still evolving.

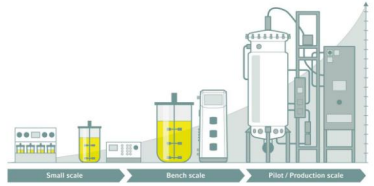


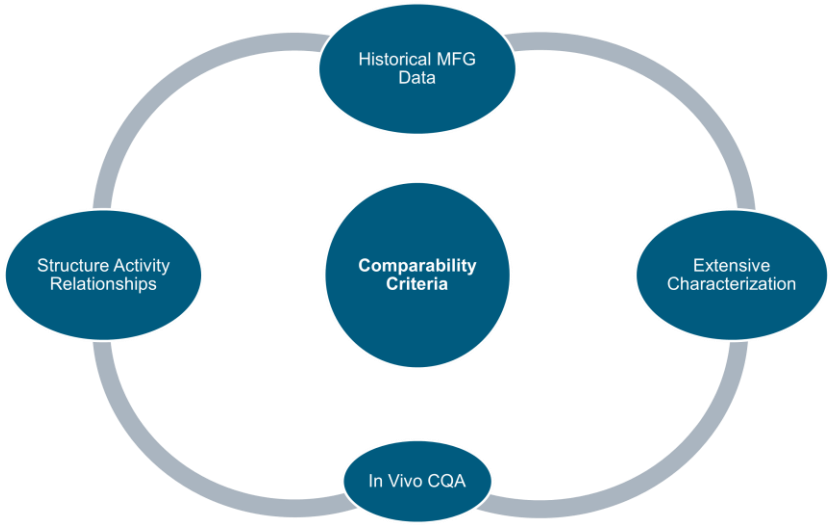
Session Overview

- Session 1 (35 min): Comparability Strategy and Rationale for Process Changes
- Session 2 (40 min): Scale-up Gaps and Solutions

Notes Distribution

Fill out form with contact information for receipt of post-session notes

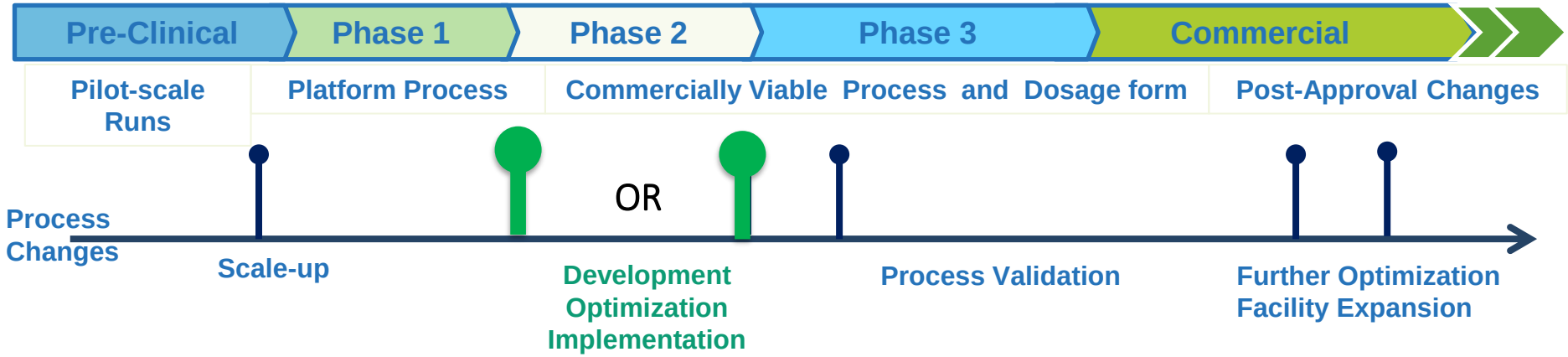




Comparability

Comparability Case Study: Major Process Change During Ph3 Trial

Typical Approach

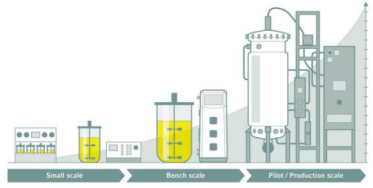


Late-Stage Process Changes

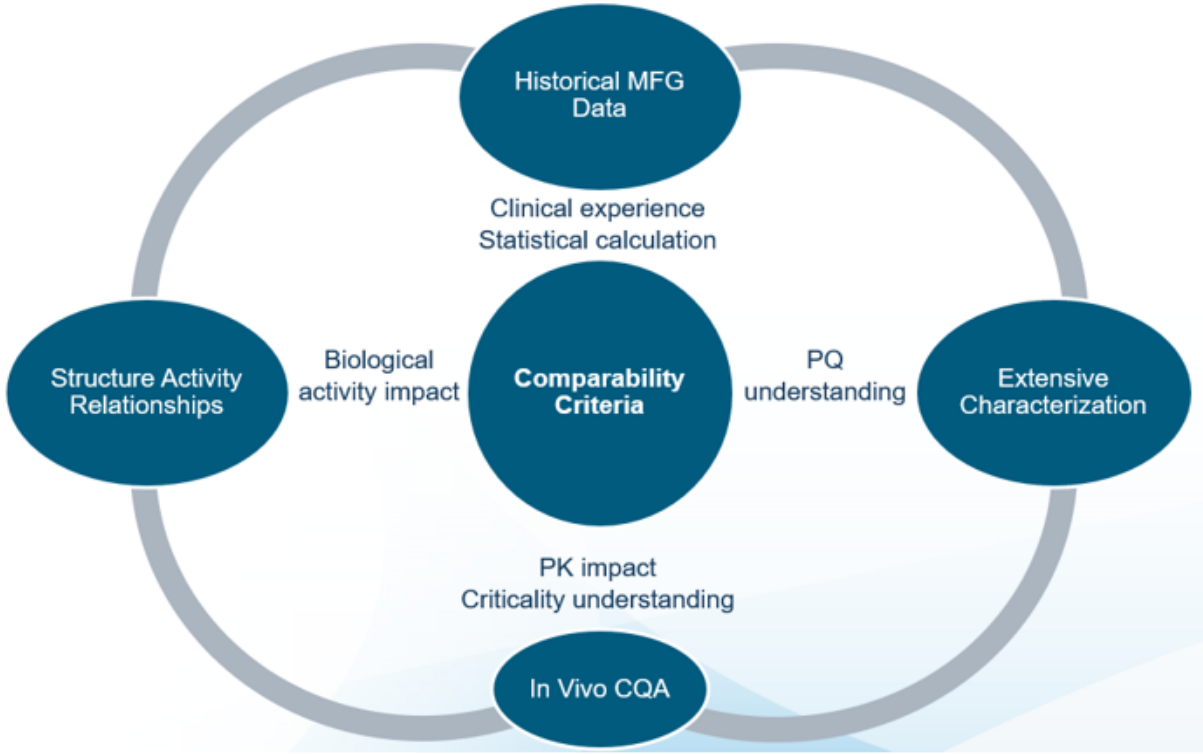
Upstream Changes Introduced:

- New MCB
- 8x MFG Scale-up
- N-stage duration
- Media & Feeds

Approach: Apply risk-based comparability plan and engage health authorities for advice to understand potential impact on program timelines



Comparability Approach



Comparability Plan

- Consistent with ICH Q5E principles
- Include pre-defined comparability criteria

Extensive Product Understanding

Justification of comparability ranges outside of clinical experience is based on product understanding

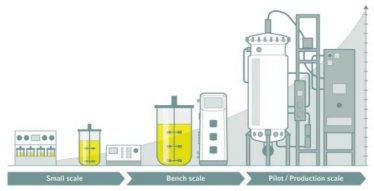
- in vivo CQA studies

Seek Regulatory Advice

- Feedback:
  - Clinical study not required but recommended
  - Use of pre-approved change protocol not endorsed. Comparability is a review issue.

<u>Specific example outcome:</u>

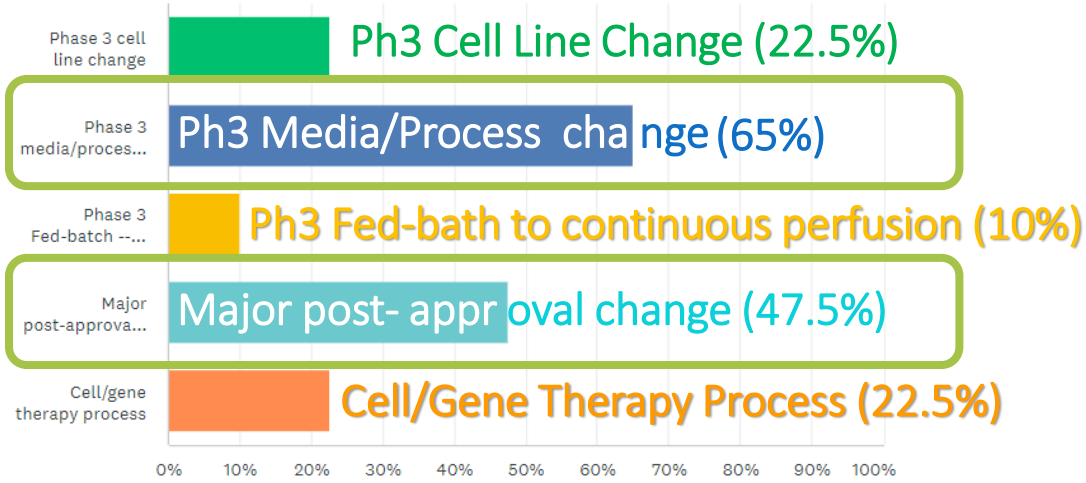
- Post-change material met the pre-determined comparability criteria
  - Structure Activity Relationship results demonstrated no impact on binding and activity
  - In vivo CQA study provided additional support of CQA criticality assessment
- Comparability package accepted and product later approved
- Material was utilized in an ongoing Phase 3 LTE trial



Survey: Comparability Experience

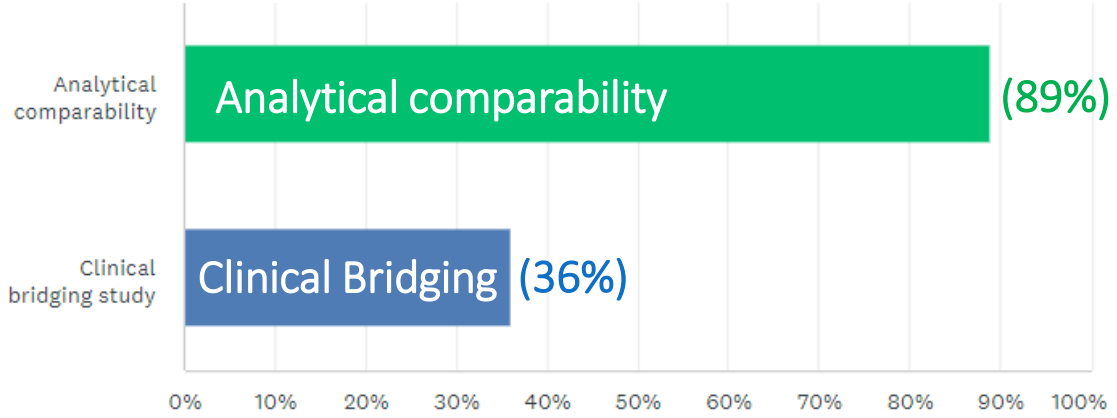
Has your company successfully filed a comparability package for the following scenarios? (Select as many as are applicable)

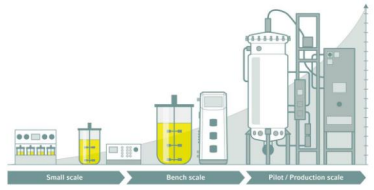
Answered: 40 Skipped: 289



For the above scenario, how did you support the process change? (Select all that apply)

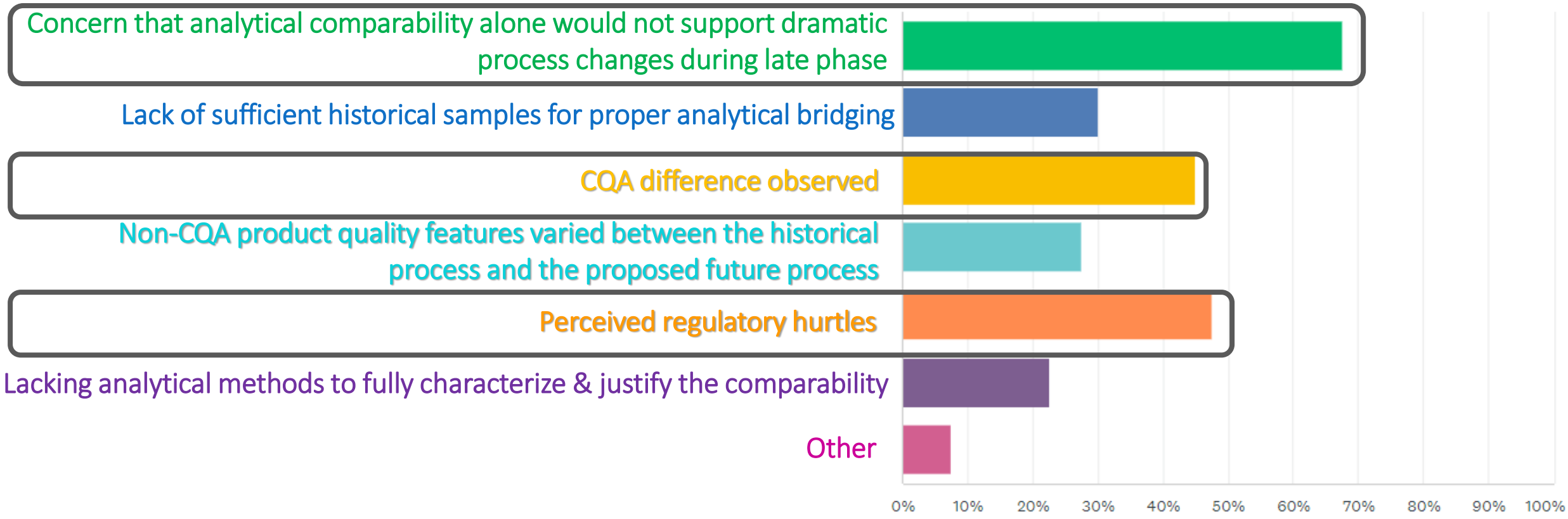
Answered: 36 Skipped: 293

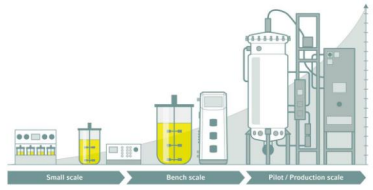




Survey: Challenges Experienced

What, if any, challenges did you experience in considering the prior scenarios? (Select as many as apply)



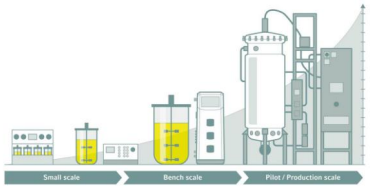


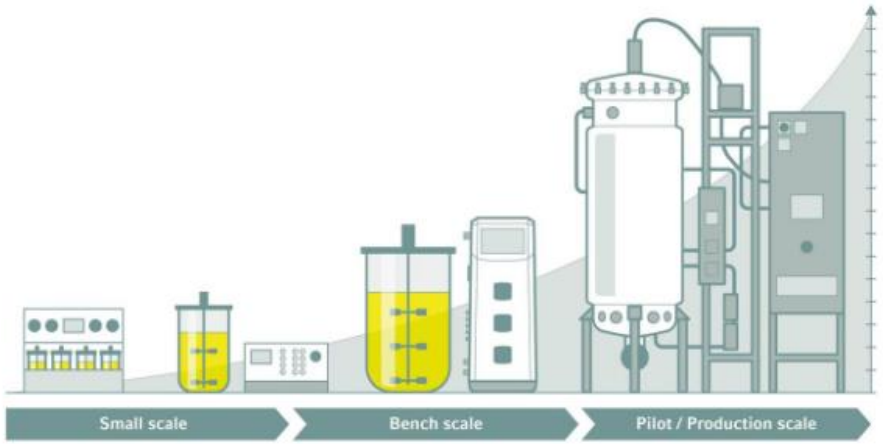
Session 1: Comparability Strategy and Rationale for Process Changes

1. Gather around the flip chart for the process change scenario you'd like to discuss
   A. Phase 1 to Pivotal trial - scale and significant process change (gene therapy)
   B. Phase 1 to Pivotal trial - scale and significant process change (cell therapy)
   C. Mid-Phase 3 media and scale change
   D. Mid-Phase 3 cell line change
   E. Major process change post-approval (e.g., cell line change)
   F. Change from fed-batch to continuous pre- or post-approval

2. For your scenario, discuss the following as a team (~17 min)
   - Comparability rationale justification – what data and information was used, was clinical bridging included?
   - Outcome and/or regulatory feedback on approach
   - Lessons learned (how would you have done this differently retrospectively or apply learnings to future programs)

3. When time is up, pick someone in your group to summarize the key points of your discussion (3 min / topic, ~18-20min total)

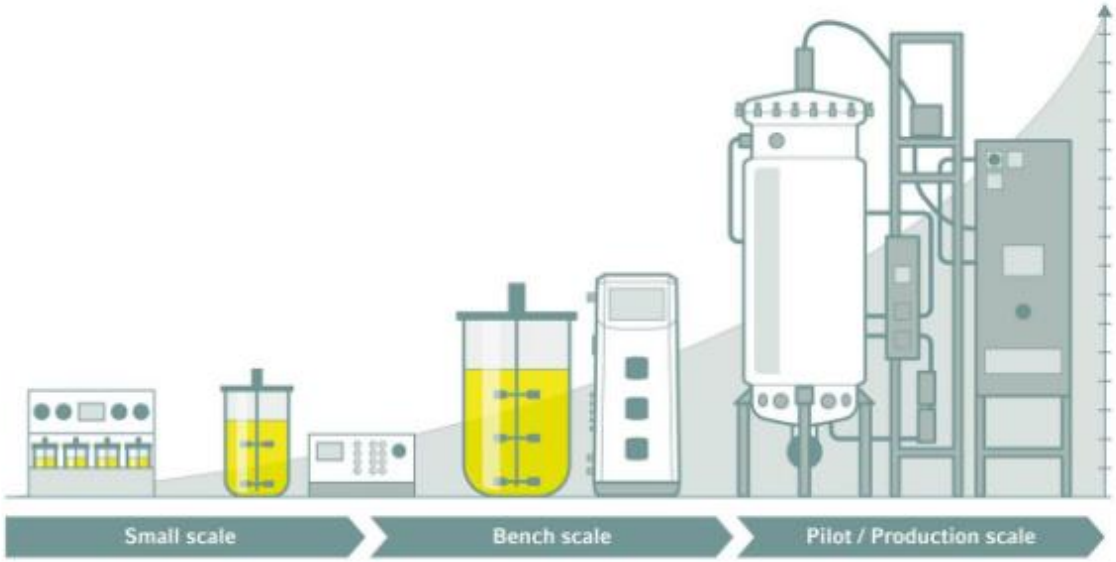




Scale-up Strategy

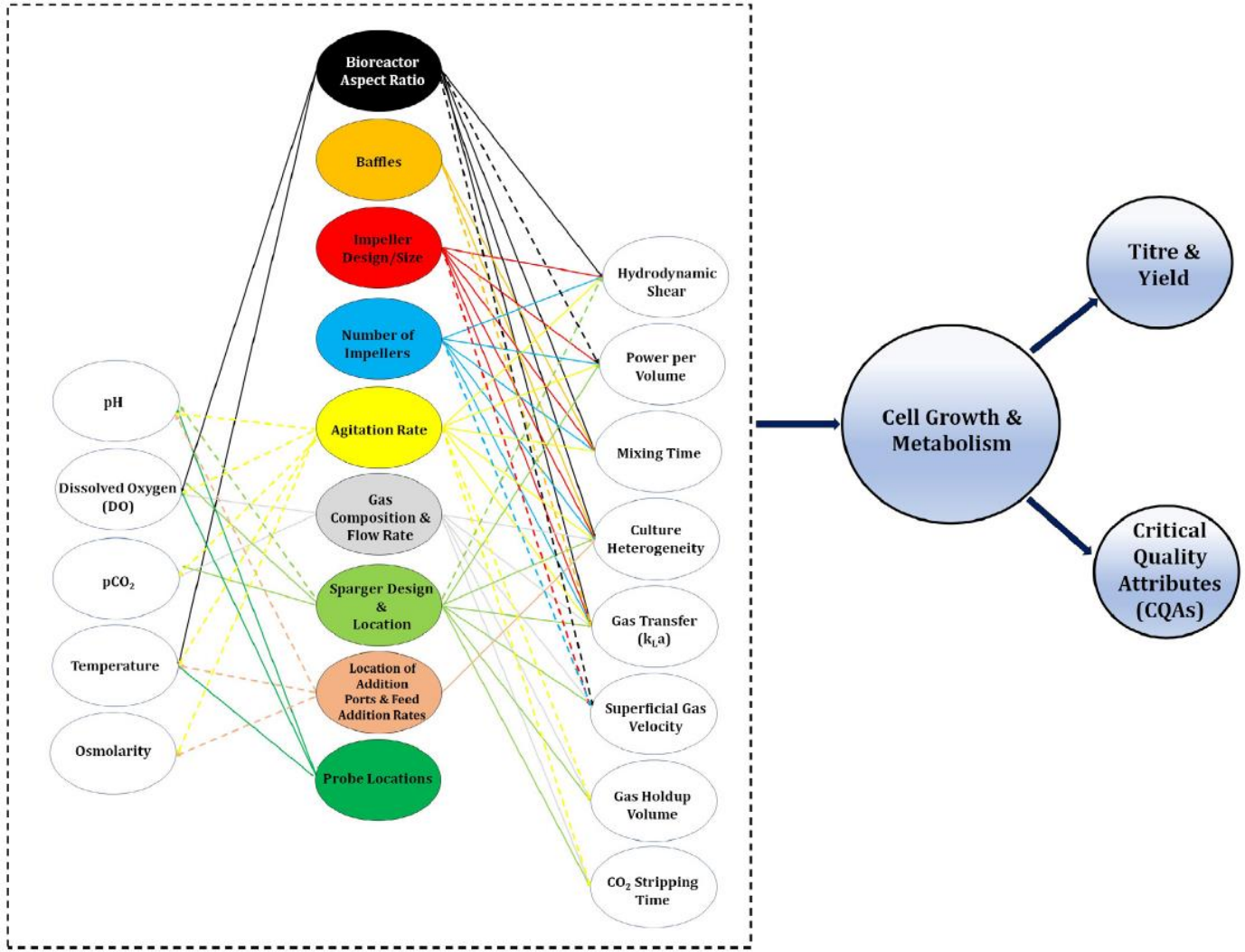
Scale-up Approaches for Cell Culture Processes

- Many cell culture process parameters generally remain constant regardless of scale, e.g., pH, temperature, DO, seeding density, harvest criteria, etc.
- Scale-dependent parameters such as agitator speed and gas flow rates are typically set by matching scaling factors such as kLa, vvm, P/V, etc. across scales
- Scale-up can be further aided by modeling approaches such as computational fluid dynamics (CFD), mechanistic/hybrid cell culture models, and multivariate data analysis techniques



Bioreactor Scale-up

Scale-up Parameter	Relevance to Scale-up
Mixing Time	Impacts homogeneity of culture with respect to DO, Feed, Temperature etc.
Power Input per Volume (P/V)	Measure of hydrodynamic environment between scales
Tip Speed	Measure of max. shear – generally not used as criteria for scale-up of suspension cell culture
Vessel Volumes per Minute (VVM)	Influences oxygen transfer and CO_2 stripping
Superficial Gas Velocity (Vs)	Influences oxygen transfer and CO_2 stripping
k_La	Impacts Gas-Liquid Mass Transfer – OTR, OUR and CO_2 removal

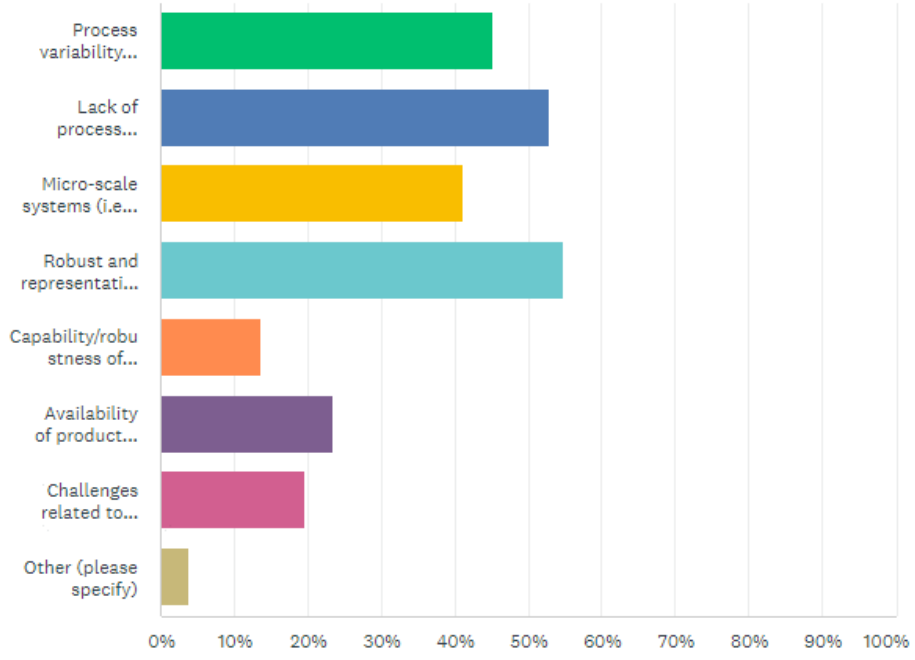


Alavijeh et al. (2022) Digital Chemical Engineering 4: 100040

Despite a long history of scaling processes in our industry, challenges remain

What gaps remain preventing 100% scale-up success rates? (select all that apply)

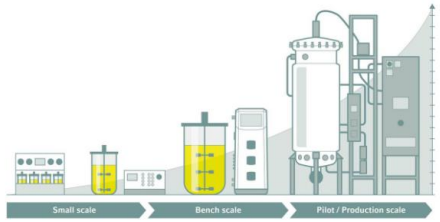
Answered: 51 Skipped: 278



ANSWER CHOICES		RESPONSES	
Process variability caused by raw materials		45.10%	23
Lack of process knowledge and characterization available for initial manufacturing scale campaigns		52.94%	27
Micro-scale systems (i.e. AMBR) not fully representative of commercial scale		41.18%	21
Robust and representative scale-down model		54.90%	28
Capability/robustness of in-process sensors		13.73%	7
Availability of product quality data		23.53%	12
Challenges related to perfusion/continuous processes		19.61%	10
Other (please specify)	Responses	3.92%	2
Total Respondents: 51			

Other

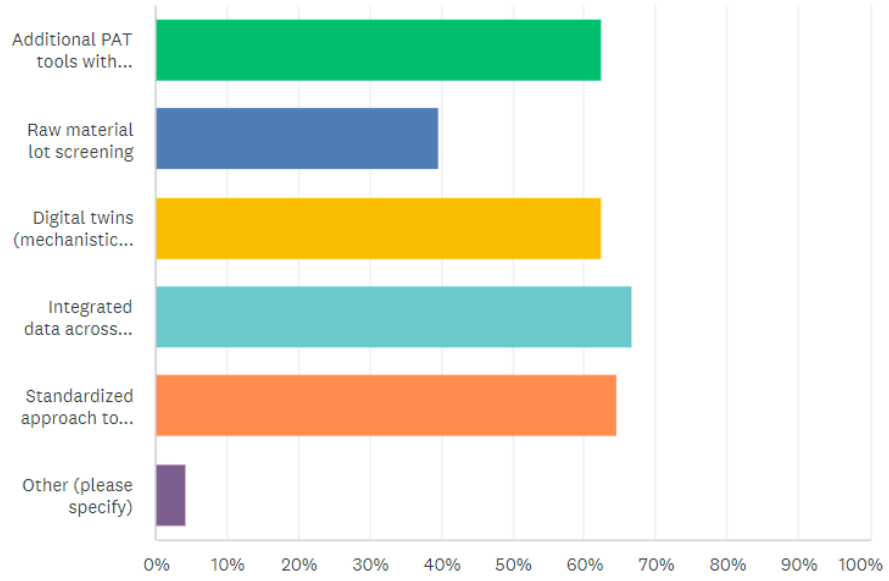
- Pace / not enough time
- Limited accuracy of analytics, differences in analytical outcomes cross site / scale / plant



Looking Toward the Future -
What's Next for Scale-up, Tech Transfer, & Comparability?

Would the following novel tools/approaches be a valuable addition to your scaleup/tech transfer strategy? (Select all that apply)

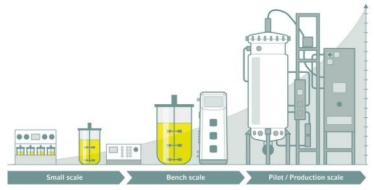
Answered: 48 Skipped: 281



ANSWER CHOICES		RESPONSES	
Additional PAT tools with feedback control (respond to process deviations in real-time)		62.50%	30
Raw material lot screening		39.58%	19
Digital twins (mechanistic and/or empirical process models to assist with development, facility transfer, process simulations, etc.)		62.50%	30
Integrated data across facilities (easy access to data for visualization)		66.67%	32
Standardized approach to equipment characterization across industry, including reactor vendors		64.58%	31
Other (please specify)	Responses	4.17%	2
Total Respondents: 48			

Other

- Shifting to more meaningful parameters (like OUR instead of VCD)
- Standardized scaledown models/approaches from vendors for SUBs

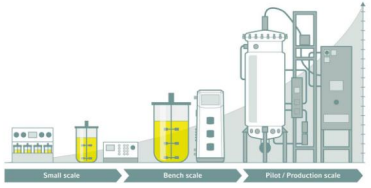


Session 2: Scale-up Gaps and Solutions

1. Gather around the flip chart for the scale-up case study you'd like to discuss (details provided on print-outs)

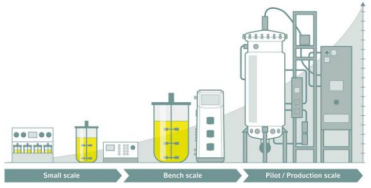
2. For your case study, discuss the following as a team (20 min)
   - What investigation steps would you take?
   - What potential root causes do you suspect?
   - Define mitigation steps
   - How to proactively avoid this in the future?
   - What tool is missing that would have prevented this scenario (Think novel, outside-the-box!)
     - What are you most excited about to implement for improved success?

3. When time is up, pick someone in your group to summarize the key points of your discussion (3 min / topic)



Case Studies

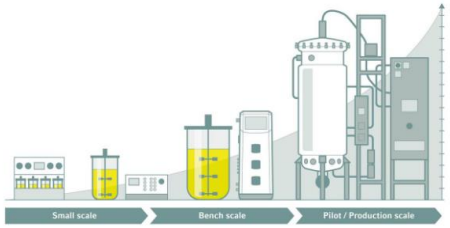
1. Scalability of media preparation
2. Transfection complexation efficiency for a gene therapy
3. Equipment design differences across facilities
4. Scale-up of an intensified process
5. Scale-up of a continuous (perfusion) process
6. Cell therapy case study



Session 2: Case Study #1

SCALABILITY OF MEDIA PREPARATION

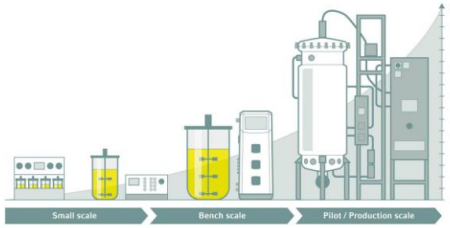
- You're scaling up a CHO cell culture process for mAb production and transferring the process to a new facility
- During the first run in the new facility, **a significant accumulation of lactate** is observed during the production bioreactor process, resulting in **reduced productivity**
- An extensive root cause analysis isolates the issue to the production media preparation. The vessel used for media prep in the new facility is significantly different from the current facility in terms of geometry, mixing characteristics, and material of construction.



Session 2: Case Study #2

COMPLEXATION SCALE-UP IN TRANSIENT TRANSFECTION (GT)

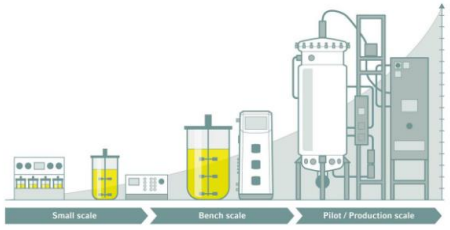
- A suspension transient transfection (sTT) process has been developed at small-scale and delivers consistent performance (cell mass, metabolism, titer).
- The process is scaling up to pilot and MFG scale (~100x and ~500x scale increase from bench respectively) to prepare for clinical material supply. (Bench-scale: 2L, pilot scale: 250L, MFG scale: 1kL)
- As the process is run at pilot scale, **notable variation in batch titer is observed which is further exacerbated at MFG scale**. The transfection cell density during the N-stage reactor is comparable.



Session 2: Case Study #3

EQUIPMENT DESIGN DIFFERENCES ACROSS FACILITIES

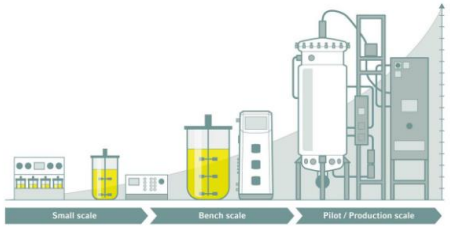
- You're transferring a CHO cell culture process for mAb production from a facility that uses 2,000-L single-use bioreactors to a facility with 20,000-L stainless steel bioreactors. In addition to the different materials of construction, there are significant differences in the design/geometry of the bioreactors in each facility.
- Due to an accelerated timeline, there is no opportunity for shakedown/engineering batches in the new facility
- Unfortunately, the first GMP batch at the 20,000-L scale **results in a change in the mAb glycosylation profile, which is a critical quality attribute** for the molecule



Session 2: Case Study #4

SCALE-UP OF AN INTENSIFIED PROCESS

- To increase productivity, you intensify an existing fed-batch process by adding ATF at N-1. However, this is an in-licensed program, so it's the first time you've used this particular CHO host and media platform.
- The process performs robustly at bench scale and routinely meets cell density, viability, and duration targets. The bench scale production reactor inoculated from the intensified N-1 also performs consistently.
- When you scale the process up to the manufacturing facility, **the N-1 takes two days longer to reach transfer criteria compared to the bench scale**. **A decline in viability** compared to the bench scale is also observed.
- In the manufacturing facility, **the production bioreactor does not achieve the desired peak cell density and productivity** that was demonstrated at bench scale.

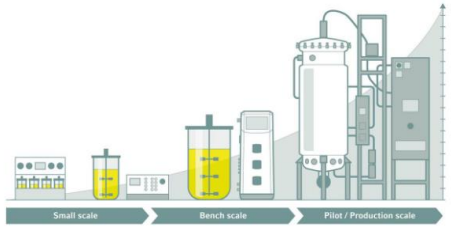


Session 2: Case Study #5

CONTINUOUS PERFUSION SCALE-UP FROM BENCH TO MFG SCALE

- To increase volumetric productivity, a process is changed from historical fed-batch platform to continuous perfusion via ATF
- Development is performed at bench-scale and process is scaled ~100x into the manufacturing facility
- Scale-up parameters applied consisted of mimicking CSPR, filter loading, filter flux, shear rates and standard bioreactor operating parameters (temp, DO, pH, aeration, etc.)
- Upon scale-up, a viability decline was more rapidly observed although growth and metabolic profiles were maintained. A slightly lower qp was also observed.
- Sieving efficiency declined earlier and more rapidly. Filter performance declined to a point requiring more frequent and less effective filter change-outs than anticipated by small-scale work.

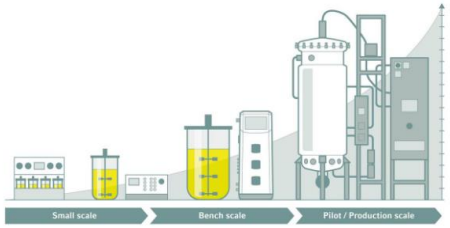
Reference: NIIMBL, *N-mAb: A case study to support development and adoption of integrated continuous bioprocesses for monoclonal antibodies Version 1*, N.I.f.I.i.M. Biopharmaceuticals, Editor. 2022: www.N-mab.org.



Session 2: Case Study #6

CELL THERAPY PROCESS CHALLENGES - PICK ONE (OR MORE) SCENARIOS TO DISCUSS

- You're using existing mammalian culture facility equipment for a cell therapy application and observe **poor viability and growth** likely due to cell sensitivity to shear stress. What special characteristics should we consider in bioreactors for the cell therapy field?
- Cell viability is used to determine the clinical dose of DP (total transduced and viable cells = total cells x transduction efficiency x % viability). However, a 20% bias is measured between the old and new viability methods: t**he old method measures 100% viability, the new measures 80% viability**. Thus, DP vials that are formulated to contain the target dose of transduced, viable cells will contain different amounts of total cells depending on which viability method is used.
- A bioreactor process is successfully established at 50-100L scale. But we experienced issues with viabilities due to prolonged exposure of the cells to cryomedia, due to the **time it takes to do the fill and finish in vials.**



Thank You!!

We hope you learned something new in the areas of comparability and scale-up.

Next Steps: Notes will be sent to all attendees who filled out form with email address submitted.

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Advances and Challenges with Tech Transfer, Scale-up, and Comparability

Fill out form with contact information for receipt of post-session notes

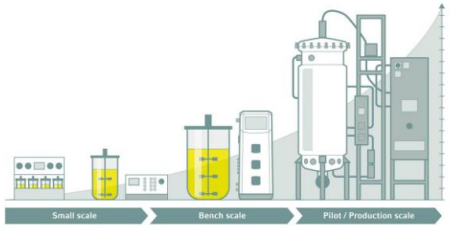
CCE Workshop 1 Attendees

Part A: Comparability Strategy and Rationale for Process Changes

1. Phase 1 to Pivotal trial - scale and significant process change (gene therapy)
2. Phase 1 to Pivotal trial - scale and significant process change (cell therapy)
3. Mid-Phase 3 media and scale change
4. Mid-Phase 3 cell line change
5. Major process change post-approval (i.e. cell line change)
6. Change from fed-batch to continuous pre- or post-approval

Part B: Scale-up Gaps and Solutions

1. Tech transfer and scalability of media Prep.
2. Transfection complexation efficiency for a gene therapy
3. Equipment design differences across facilities
4. Scale-up of an intensified process
5. Scale-up of a continuous (perfusion) process
6. Cell therapy case study



Advances & Challenges with Tech Transfer, Scale-up, and Comparability

Part 1: Comparability Strategy and Rationale for Process Changes

Discussion Questions

- Comparability rationale justification – what data and information was used, was clinical bridging included?
- Outcome and/or regulatory feedback on approach
- Lessons learned (how would you have done this differently retrospectively or apply learnings to future programs)

Highlights / Key Points

- Seek Regulatory feedback proactively
- Leverage analytical comparability only (i.e., no clinical bridging) whenever possible. Characterize and show when attributes that may have changed do not have a biological impact on the molecule effectiveness.
- Some experiences erred on the side of caution and leveraged clinical bridging even in situations where the agency had not formally requested that.
- Make decision on clinical bridging based on comparability outcome and Regulatory feedback
- When making the decision to invest in a major process change, consider and balance the effort, cost, resources vs the ROI gained from the change once implemented.
- For a cell line change – only do it if necessary, but commit to the decision and resource for success
- Impact of process changes on clinical efficacy can be particularly difficult to assess for cell therapies
- For gene therapy, the 'process is the product' situation is still applicable, so minimize changes and justify them as best as possible with data.

Part 2: Scale-up Gaps and Solutions

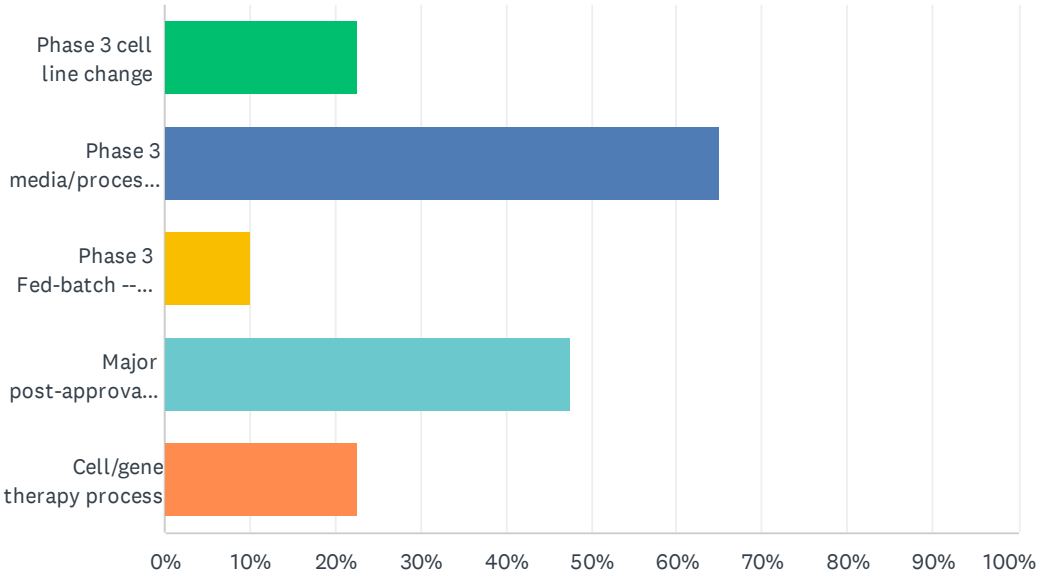
Five case studies were shared covering a variety of scenarios (media prep, equipment design differences, intensified process, continuous perfusion, gene therapy transfection efficiency).

Highlights / Key Points

- Full vessel characterization (mass transfer, mixing, CFD, etc.) is key to support successful scale-up, especially to large (15-20kL) stainless steel vessels
- For ATF-intensified processes, consider potential differences in the time cells are spending outside the bioreactor across scales
- Different scale-down models may be needed for different aspects of scale-up, especially for intensified/complex processes
- Data monitoring, mining, and access to data or operational details within the MFG setting is valuable and needs improvement in many cases.
- Future areas of investment desired: raw materials testing, inline PAT tools, digital twins, at-scale engineering runs including media prep test batches

Q5 Has your company successfully filed a comparability package for the following scenarios? (Select as many as are applicable)

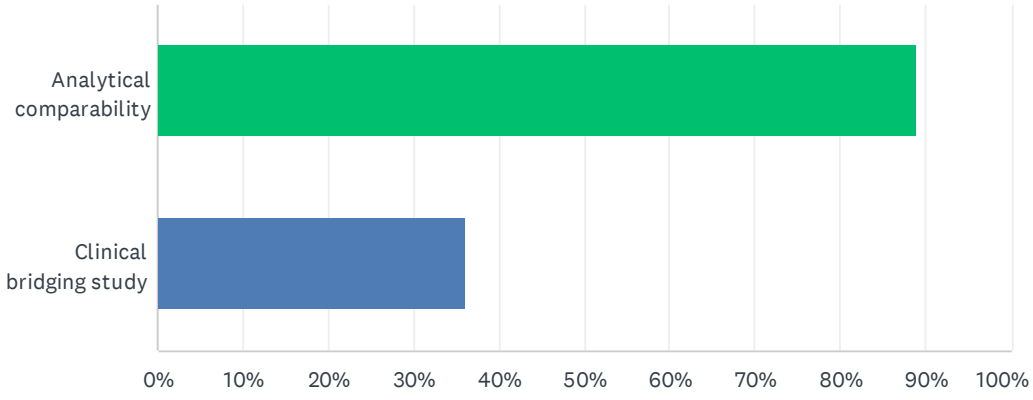
Answered: 40 Skipped: 289



ANSWER CHOICES	RESPONSES	
Phase 3 cell line change	22.50%	9
Phase 3 media/process change	65.00%	26
Phase 3 Fed-batch --> perfusion change	10.00%	4
Major post-approval change, e.g., 2nd gen process	47.50%	19
Cell/gene therapy process	22.50%	9
Total Respondents: 40		

Q6 For the above scenario, how did you support the process change? (Select all that apply)

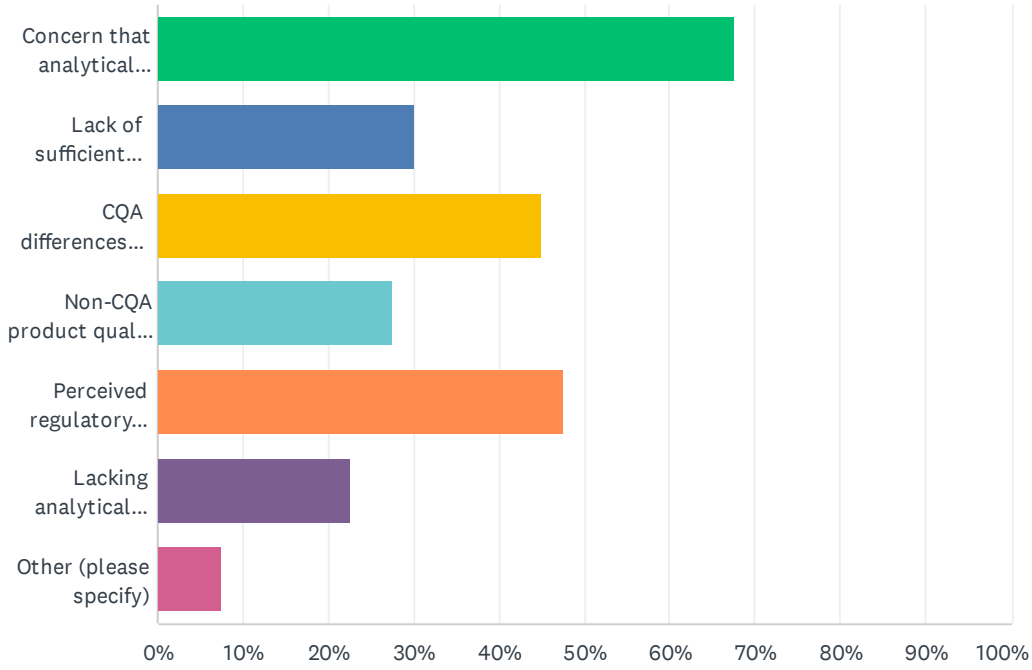
Answered: 36 Skipped: 293



ANSWER CHOICES	RESPONSES	
Analytical comparability	88.89%	32
Clinical bridging study	36.11%	13
Total Respondents: 36		

Q7 What, if any, challenges did you experience in considering the above scenarios? (Select as many as apply)

Answered: 40 Skipped: 289

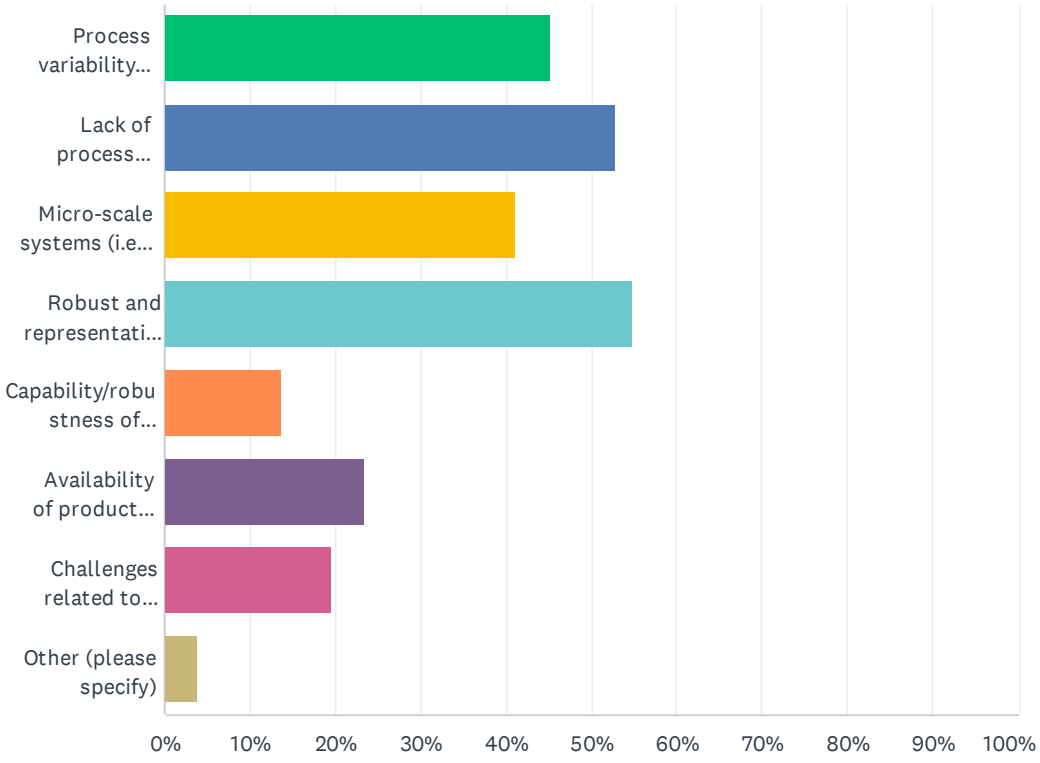


ANSWER CHOICES	RESPONSES	
Concern that analytical comparability alone would not support dramatic process changes during late phase	67.50%	27
Lack of sufficient historical samples for proper analytical bridging	30.00%	12
CQA differences observed	45.00%	18
Non-CQA product quality features varied between the historical process and the proposed future process	27.50%	11
Perceived regulatory hurtles	47.50%	19
Lacking analytical methods to fully characterize and justify the comparability	22.50%	9
Other (please specify)	7.50%	3
Total Respondents: 40		

#	OTHER (PLEASE SPECIFY)	DATE
1	None	4/13/2023 1:22 AM
2	None	4/13/2023 1:03 AM
3	Limited accuracy of available analytical (offline) methods for process control; limited meaning of standard parameters	4/3/2023 2:02 AM

Q8 What gaps remain preventing 100% scale-up success rates? (select all that apply)

Answered: 51 Skipped: 278

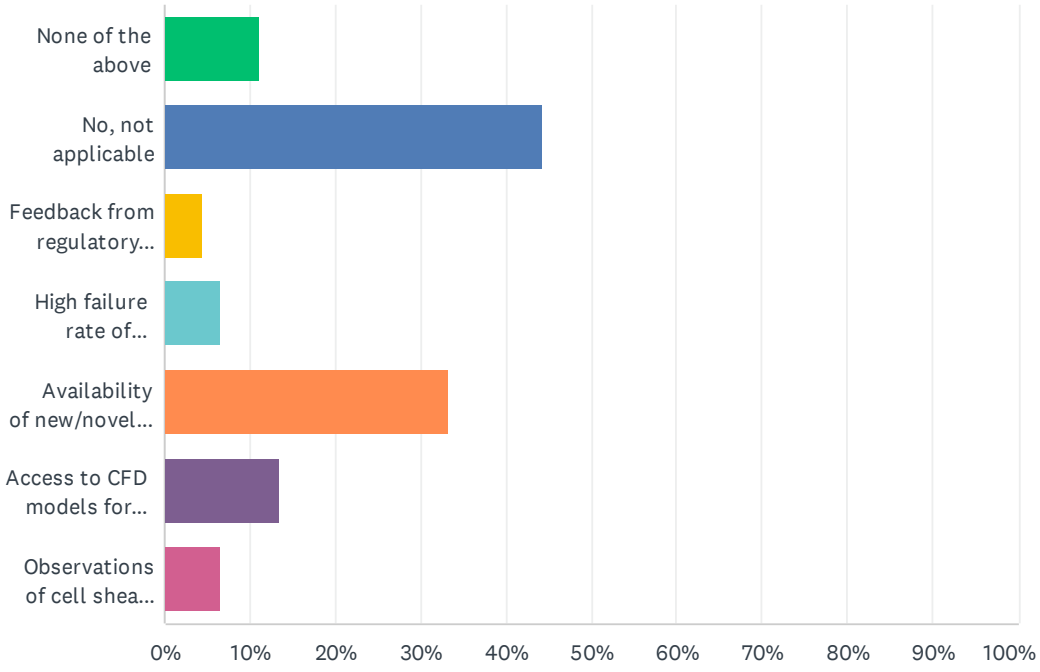


ANSWER CHOICES	RESPONSES	
Process variability caused by raw materials	45.10%	23
Lack of process knowledge and characterization available for initial manufacturing scale campaigns	52.94%	27
Micro-scale systems (i.e. AMBR) not fully representative of commercial scale	41.18%	21
Robust and representative scale-down model	54.90%	28
Capability/robustness of in-process sensors	13.73%	7
Availability of product quality data	23.53%	12
Challenges related to perfusion/continuous processes	19.61%	10
Other (please specify)	3.92%	2
Total Respondents: 51		

#	OTHER (PLEASE SPECIFY)	DATE
1	Pace / not enough time	4/4/2023 11:06 AM
2	Limited accuracy of analytics, differences in analytical outcomes cross site / scale / plant	4/3/2023 2:02 AM

Q9 Has your company modified your scale-up approach in recent years? If yes, what were the drivers? (Select all that apply)

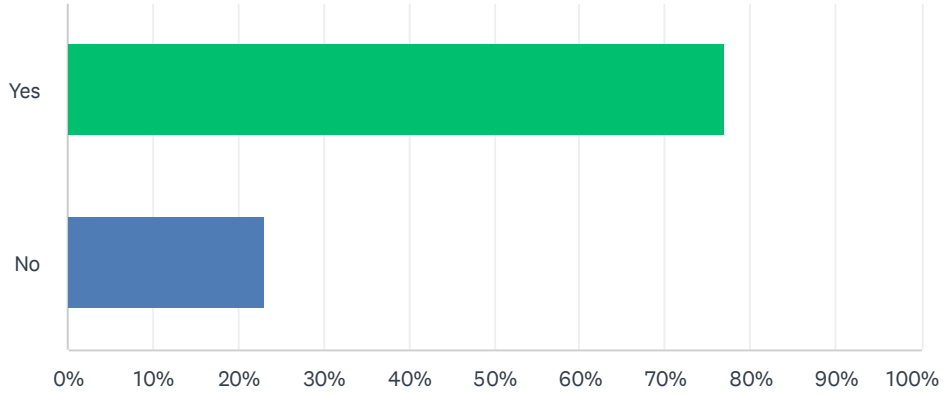
Answered: 45 Skipped: 284



ANSWER CHOICES	RESPONSES	
None of the above	11.11%	5
No, not applicable	44.44%	20
Feedback from regulatory agencies	4.44%	2
High failure rate of previous approach	6.67%	3
Availability of new/novel approach	33.33%	15
Access to CFD models for equipment	13.33%	6
Observations of cell shear damage	6.67%	3
Total Respondents: 45		

Q10 Do you have a defined platform process?

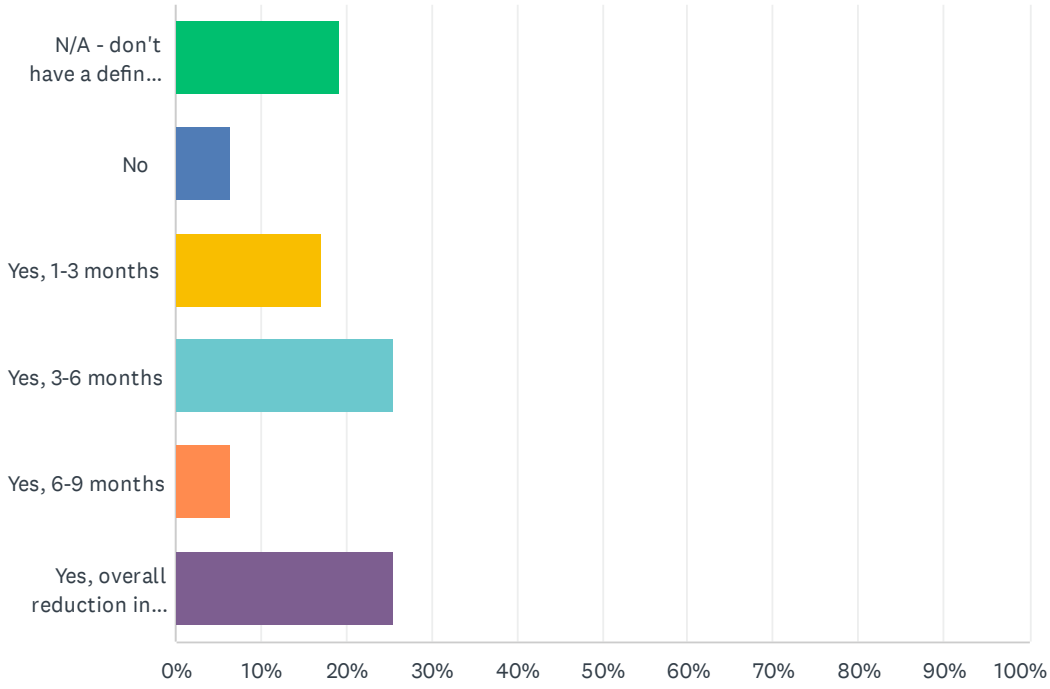
Answered: 52 Skipped: 277



ANSWER CHOICES	RESPONSES	
Yes	76.92%	40
No	23.08%	12
TOTAL		52

Q11 Have platform processes reduced time investment in process development, tech transfer, etc.? (Select one)

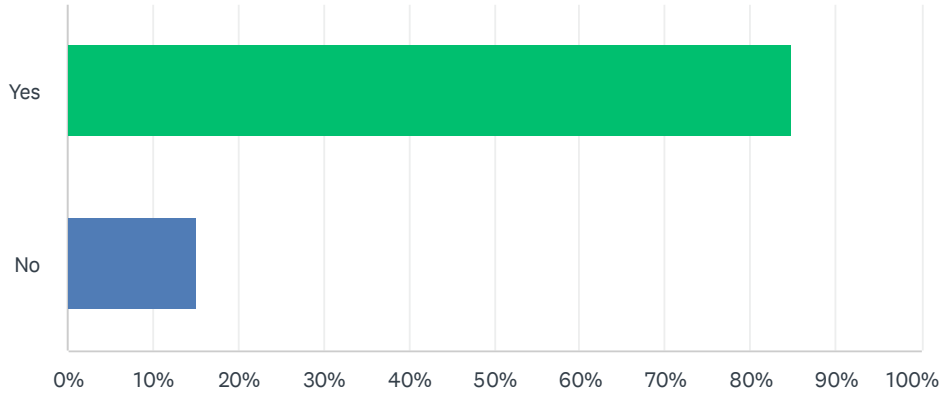
Answered: 47 Skipped: 282



ANSWER CHOICES	RESPONSES	
N/A - don't have a defined platform	19.15%	9
No	6.38%	3
Yes, 1-3 months	17.02%	8
Yes, 3-6 months	25.53%	12
Yes, 6-9 months	6.38%	3
Yes, overall reduction in resources but no change in program timeline	25.53%	12
TOTAL		47

Q12 Have platform processes improved your scale-up/tech transfer success rate?

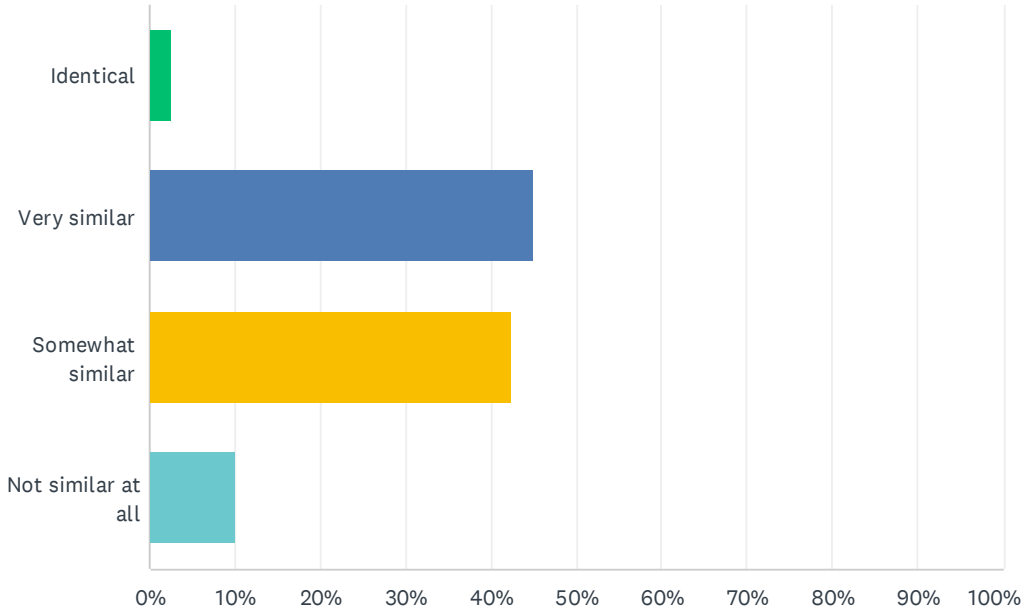
Answered: 46 Skipped: 283



ANSWER CHOICES	RESPONSES	
Yes	84.78%	39
No	15.22%	7
TOTAL		46

Q13 In general, how similar is your FIH process to your Ph3/commercial process? (Select one)

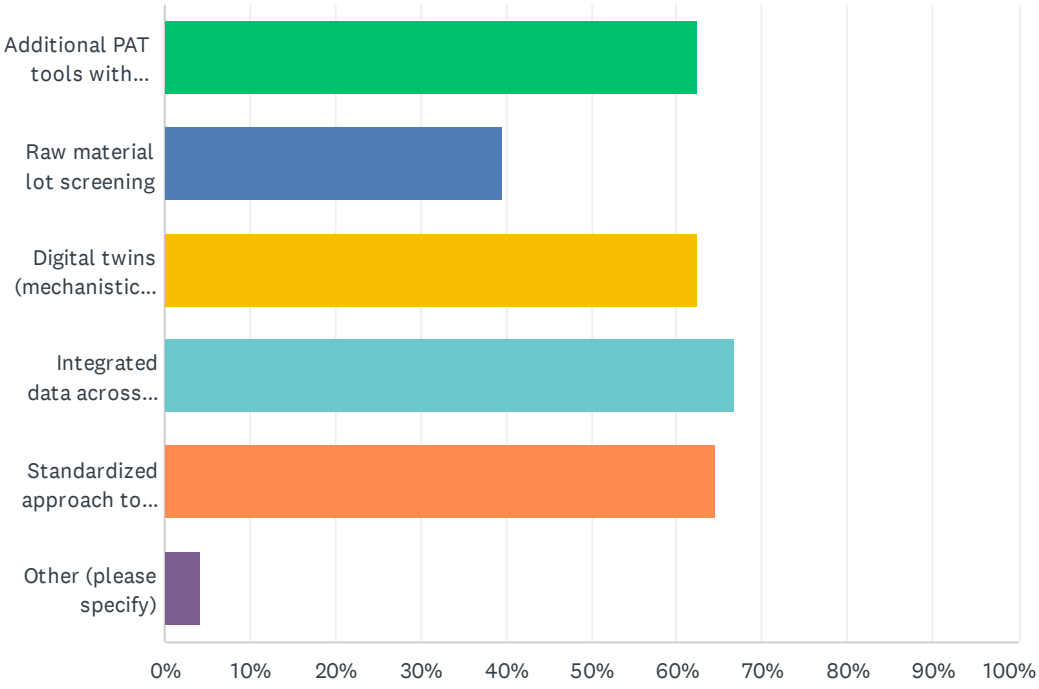
Answered: 40 Skipped: 289



ANSWER CHOICES	RESPONSES	
Identical	2.50%	1
Very similar	45.00%	18
Somewhat similar	42.50%	17
Not similar at all	10.00%	4
TOTAL		40

Q14 Would the following novel tools/approaches be a valuable addition to your scaleup/tech transfer strategy? (Select all that apply)

Answered: 48 Skipped: 281



ANSWER CHOICES	RESPONSES	
Additional PAT tools with feedback control (respond to process deviations in real-time)	62.50%	30
Raw material lot screening	39.58%	19
Digital twins (mechanistic and/or empirical process models to assist with development, facility transfer, process simulations, etc.)	62.50%	30
Integrated data across facilities (easy access to data for visualization)	66.67%	32
Standardized approach to equipment characterization across industry, including reactor vendors	64.58%	31
Other (please specify)	4.17%	2
Total Respondents: 48		

#	OTHER (PLEASE SPECIFY)	DATE
1	Shifting to more meaningful parameters (like OUR instead of VCD)	4/3/2023 2:02 AM
2	Standardized scaledown models/approaches from vendors for SUBs	4/2/2023 4:45 PM