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Regulatory challenges of continuous biomanufacturing

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REGULATORY CHALLENGES OF CONTINUOUS BIOMANUFACTURING

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Agenda

Regulatory Challenges/Considerations

- Myth – batch definition challenge
- With new approaches and emerging technologies, engage FDA early and often
- With changing regulatory environment –need internal alignment first
- With legacy unique processes or products – embrace education of agency and re-education of agency reviewers
- Case study - validation of hybrid continuous biomanufacturing process
- Conclusions

Myth – Batch Definition Challenge

- Many batch CFR requirements – especially batch traceability to product defect or recall delineation
- Fed-batch process results in easily identifiable discrete unit
- On first appearance, continuous manufacturing of drugs – either drug product* or drug substance, doesn't lend itself to easily identifiable discrete unit
- However, batch can be defined by time or mass interval, resulting in discrete unit of time or mass, according to FDA

*FDA recently approved first continuous drug product manufacturing (Orkambi®) in 2015 based on time-based interval

Regulatory Challenges/Considerations

- With new approaches and emerging technologies, engage FDA early and often
  - Facility-wide rapid microbiological testing for bioburden control
  - New biotech facility designed for all disposable technology
  - First commercial fully integrated continuous biomanufacturing with PAT

Regulatory Challenges/Considerations

- With changing regulatory environment – need internal alignment first
  - Almost always, regulatory environment changes add more requirements over time
  - Fortunately some recent agency adaptive thinking (ICH Q9 - risk based assessment)
  - People set expectations based on prior experiences
    - Prior experiences fixed in time
    - Time moves on, hard to stay current with agency expectations
    - Regulatory affairs chartered to follow current agency thinking

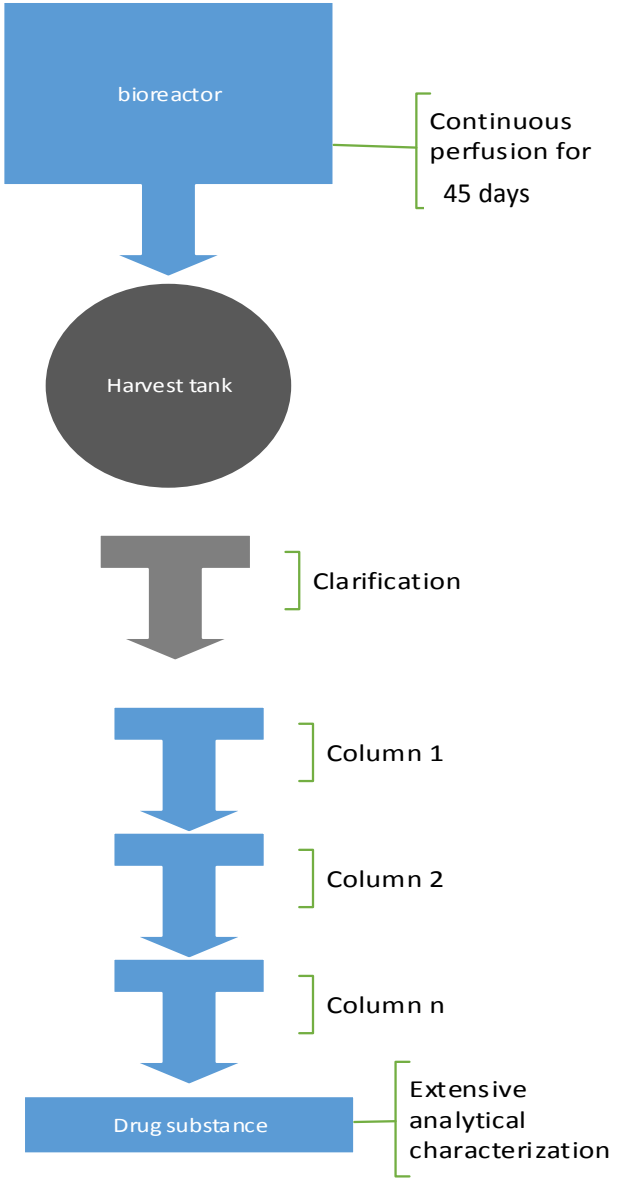
Educating New Agency Reviewers

- Agency reviewers typically well versed on mainstream practices but vary in exposure to unique systems or approaches
  - Ex., biologic/device combination product in 1990's
- In agency meetings, submissions, RTQ, etc. anticipate to educate new reviewers on products history and on characteristics of unique system

Case Study

- Legacy Perfusion Process
  - Labile product produced by hybrid continuous perfusion upstream process followed by discrete downstream process
  - Process evolution
    - Early stage to commercialization scale-up
    - Later scale-up for additional capacity

Clinical Manufacturing Process

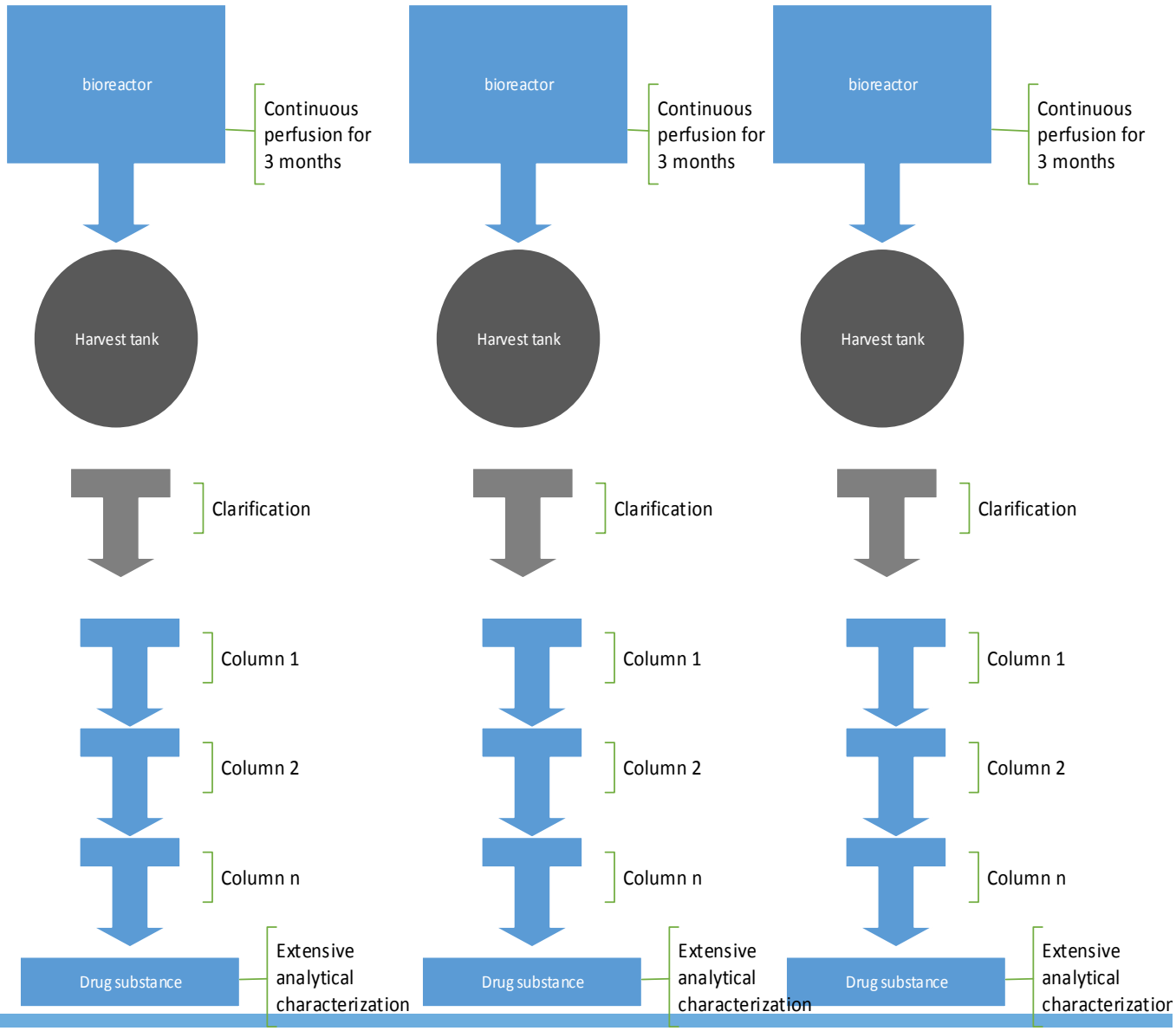


Scale Up for Commercial Capacity

Criteria

- Triple capacity
- Demonstrate CMC comparability (ICH Q5E)
- Avoid non-clinical/clinical comparability studies
  - For chronic treatment, switch to scale-up material in extension studies to evaluate safety

Commercial Process Option 1



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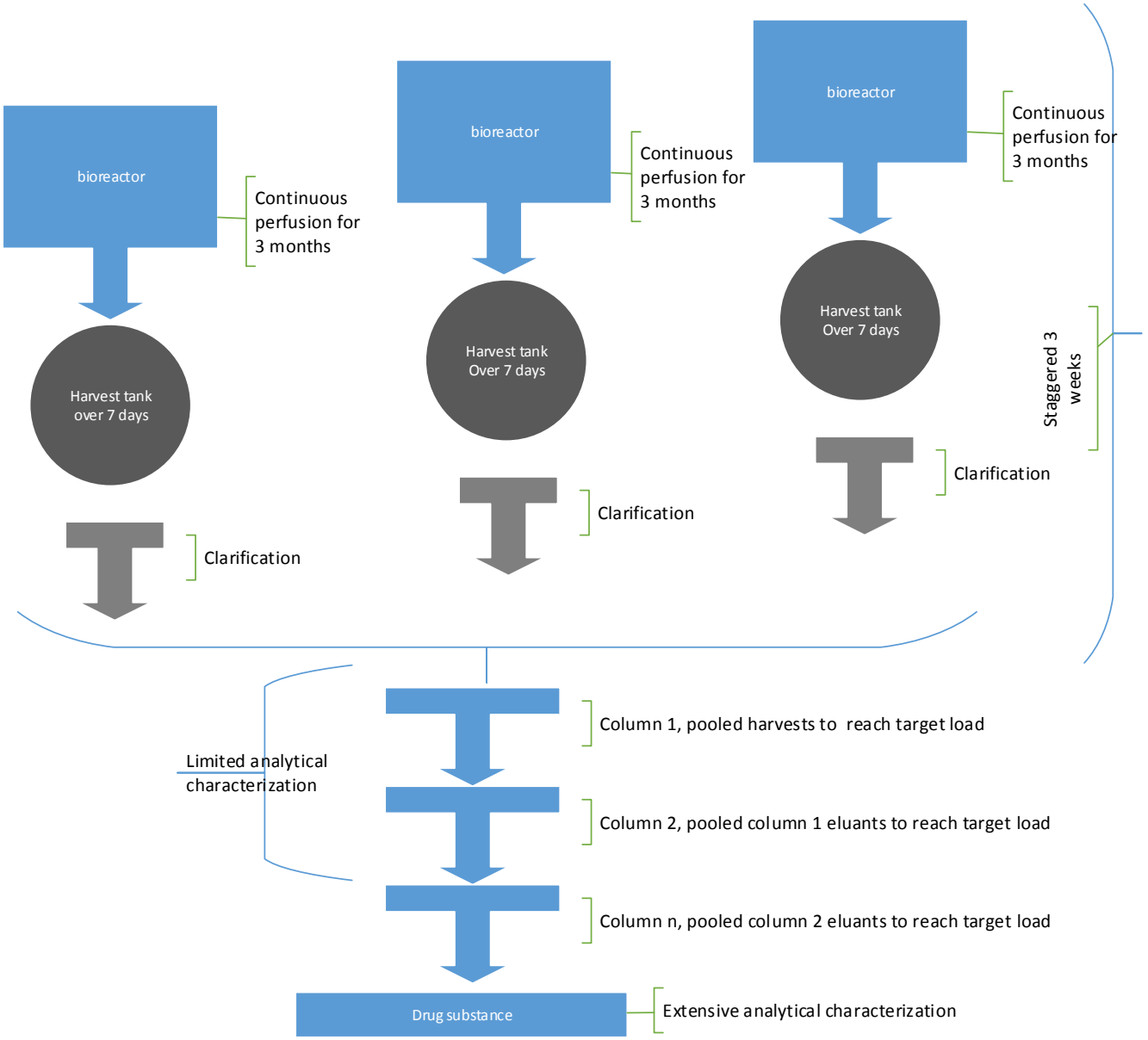
Commercial Process Option 2

Pooling
Staggered startup



Comparison

Option 1 – Three Parallel Streams

PROs

- Independence of operation
  - Provides redundancy
  - Cleaning
  - Maintenance
  - Validation

CONs

- Increased downstream hardware and operation costs

Option 2 – Shared Downstream

PROs

- Pooling smooths out individual bioreactor production output and product consistency
- Savings on downstream hardware and operations cost

CONs

- Interruption/shutdown/change to individual bioreactor(s) stream or change to approved downstream process may/would require long validation/approval cycle

Option 2 Selected

- Process Validation Considerations
  - Validation strategy
    - Three independent campaigns of integrated unit

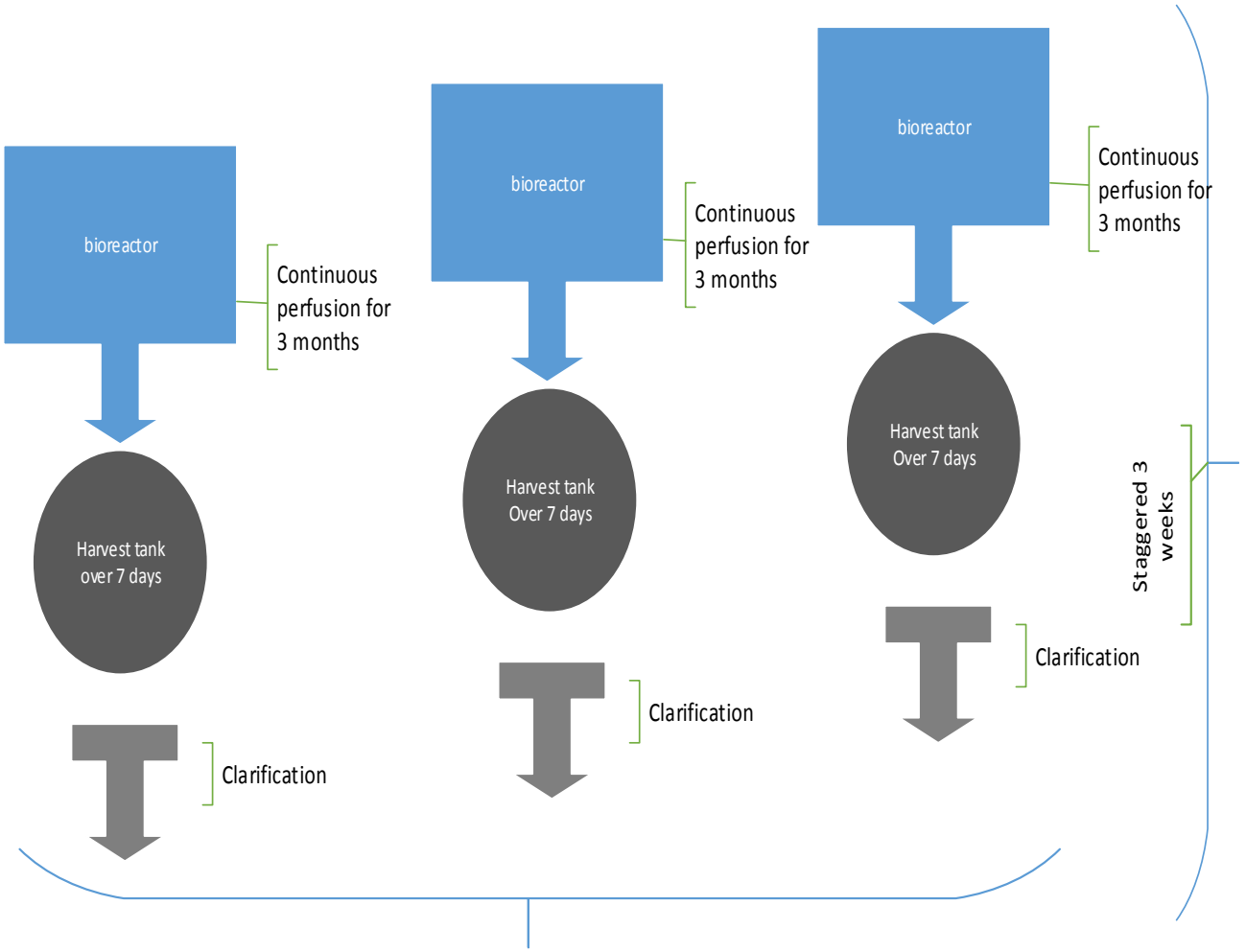
    (if Option 1, three independent campaigns of 1st bioreactor, then one campaign for 2nd bioreactor and one campaign for 3rd)
    - Total campaign cycle time
  - Cleaning validation – need to clean before/after three campaign runs

Option 2 - Upstream Campaign Time

Upstream Steps

- Inoculum build-up – 1 wks.
- 1st bioreactor production
- 2nd bioreactor – 3 wks. offset
- 3rd bioreactor – 3 wks. offset
- 1st bioreactor stopped – 3 mo.

Total upstream cycle time for commercial process: almost 5 months



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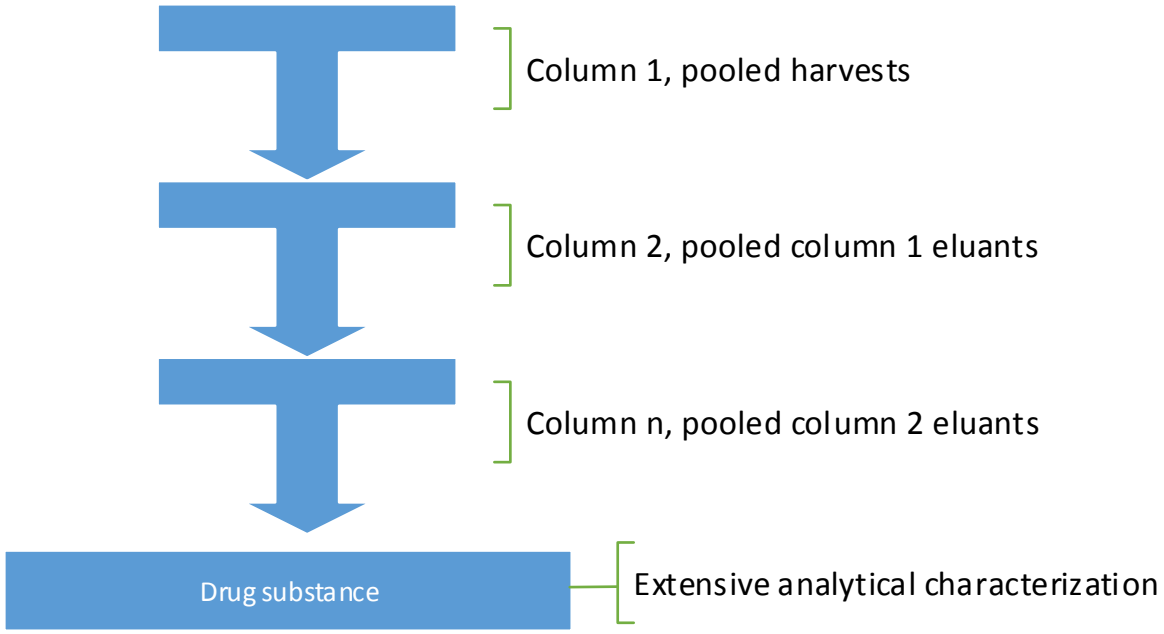
Option 2 - Downstream Campaign Time

Downstream Steps

- 3+ purification steps
- Validated hold times of 1-12 months
- Typical downstream cycle time of 8 weeks
- Can accelerate to 4 weeks



Validation Process Campaign Time Reality

Total of Campaign Upstream and Downstream Cycles

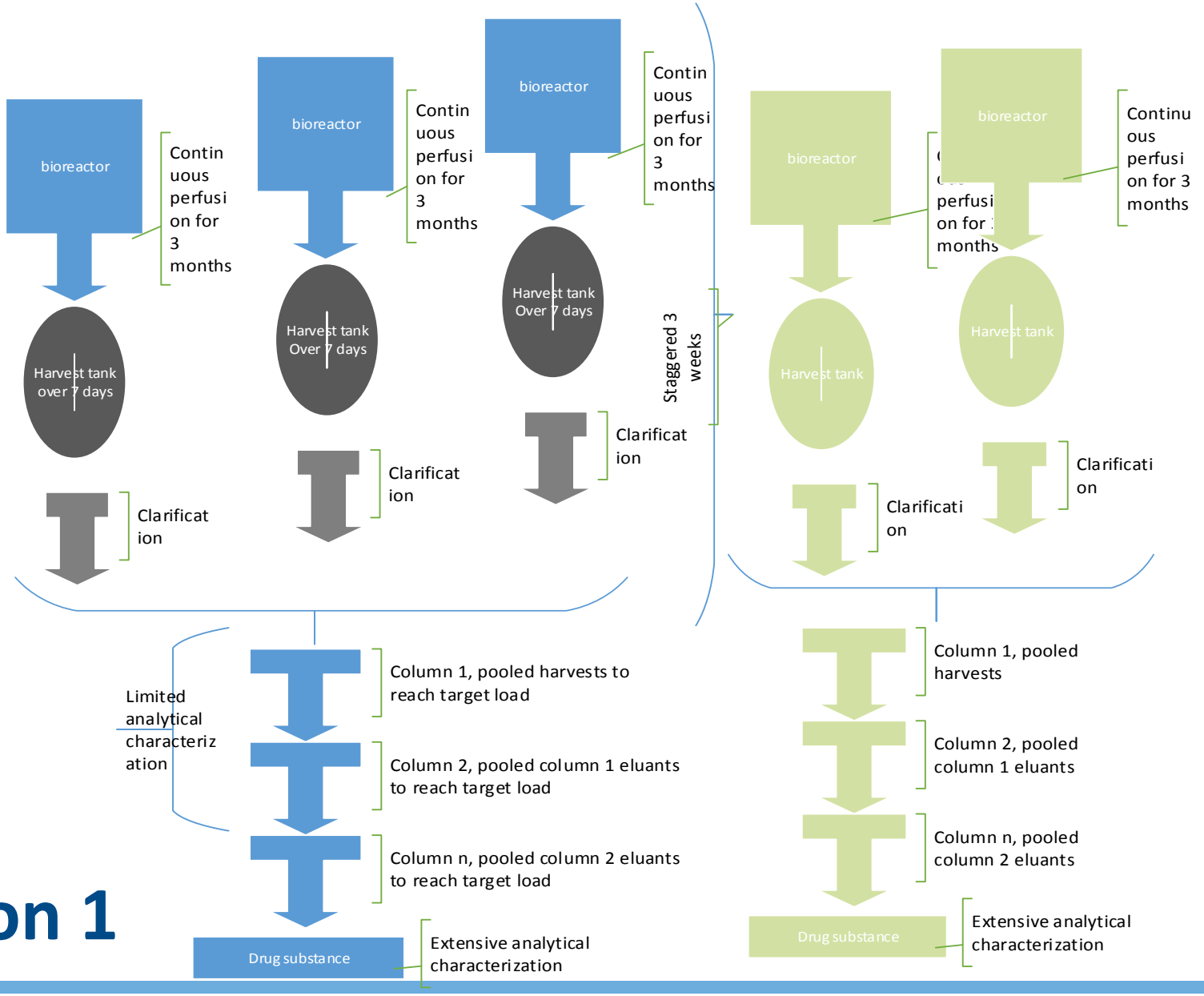
- Typical upstream cycle time of almost 5 months
- Accelerated downstream cycle time of about 1 month
- Therefore total campaign process cycle time of almost 6 months for validation process
- For 3 campaigns, complete process validation over 18 months

Product Grows – Add Additional Capacity

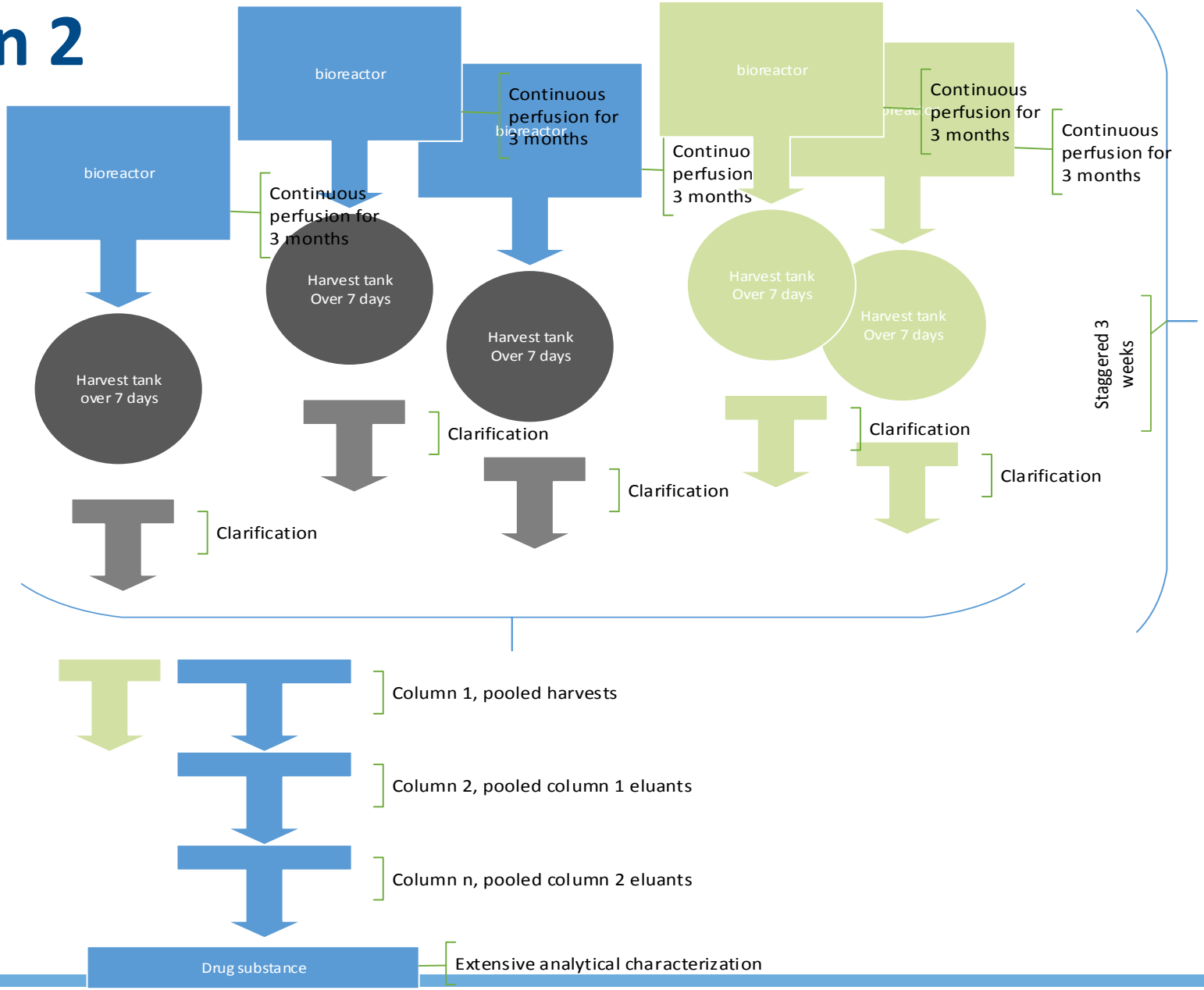
Company needs to increase commercial capacity and decides to add 2 more continuous bioreactors

- Need to add downstream capacity minimally at step 1
- Review options to expand and resulting validation, regulatory, and operational considerations
  - Comparability studies needed

Option 1



Option 2



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Comparison

Option 1 – Two Parallel Streams

PROs

- Provides some redundancy
- Independence of operation
  - Cleaning
  - Maintenance
  - Validation

CONs

- Validation of not only new upstream but also of new downstream
- Increased downstream hardware and operation cost

Option 2 – Shared Downstream

PROs

- Represents likely future commercial production (integrated)
- Pooling smooths out individual bioreactor production output and product consistency
- Savings on downstream hardware and operations cost

CONs

- Interruption/shutdown/change to individual bioreactor(s) stream or change to approved downstream process may/would require long validation/approval cycle

Option 2 Selected

- Process Validation Considerations
  - Family approach of added bioreactors
    - One independent campaign of each upstream bioreactor purified with commercial validated downstream process
    - (if Option 1, three independent campaigns of new parallel bioreactor/downstream stream)
    - Blend or no blending with validated commercial upstream
    - Risk of exposing validated downstream units to unapproved process material

Option 2 Selected

- Process Validation Considerations
  - Blend or Not-to-Blend with validated commercial stream
    - Blend option represents future commercial operations
    - Whereas not-to-blend option does not representative final commercial operations
      - Does avoid 1:5 dilutive effect of blending
      - Therefore more rigorous comparison of new bioreactor output vs. commercial
      - Preferred by FDA and EMA
      - As a result, downstream operation toggles between commercial and validation runs

Option 2 Selected

- Process Validation Considerations
  - Impact of exposing validated downstream units to unapproved process material – risk assessment
    - Cleaning validation developed for commercial product
    - Family bioreactor should produce similar and comparable product and impurity profile
    - Minimal risk

Conclusions

- Batch definition not hurdle for continuous processes with FDA
- With new approaches and emerging technologies, engage FDA early and often
- Whenever dealing with legacy unique processes or products, embrace (re)education of new agency reviewers or agency in general
- In some cases of hybrid continuous upstream manufacturing, long production cycles valuable but with validation consequences
- In choosing between parallel processing streams or combined processing streams, consider validation cycles for lifecycle management

Questions?

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