Hierarchy of High Impact Improvements in Bio Manufacturing

The National Academies of Sciences, Engineering & Medicine

Workshop on Innovations in Pharmaceutical Manufacturing

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How does innovation impact the central dogma of regulatory surveillance?

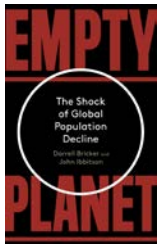
- While regulators recommend to consider certain technology, they won't tell you what to use
- What they do tell you though (and will likely continue to do) is: **"Show me the data!"**
- What will change (or will it) when **big data, proprietary modelling approaches and AI** enter biomanufacturing?

The current regulatory "dogma"

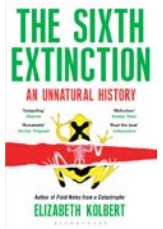
"Gretel, I think we should have left a paper trail instead of breadcrumbs."

Global Perspective on Biopharma Innovation

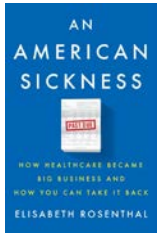
Selected Drivers for Healthcare Policy



- Irrevocable demographic change towards ageing & shrinking populations



- Human penetration of last natural resorts and new level of contact with global pathogen reservoir



- Business case versus health priority driven biopharmaceutical development & supply chain

Challenges for Industry & Regulators

- Pandemic of non-communicable diseases: e.g., cancer, diabetes, neurological disorders
- New & modified pathogens with changed medical need: e.g., from resistance and senior population
- Global disease burden secondary to pipelines, drug & vaccine shortages, affordability issues

Global Trends trigger improvement needs

Global needs and trends…

- Complexity & pace of change
- Portfolio diversification
- Business case attractiveness
  - Rare diseases in focus
  - Affordability of treatment
  - Drug & vaccine shortages

Problems to be solved…

- **Facility output** & Process yield
- **Flexibility** for portfolio & scale
- **Simplification** of operations
- **Cost** of infrastructure, quality and regulatory affairs

Path forward, the one-page summary

What are the basic features new technology needs to offer?

Max achievable productivity from a biologic facility is defined by the output per time from the installed production reactors

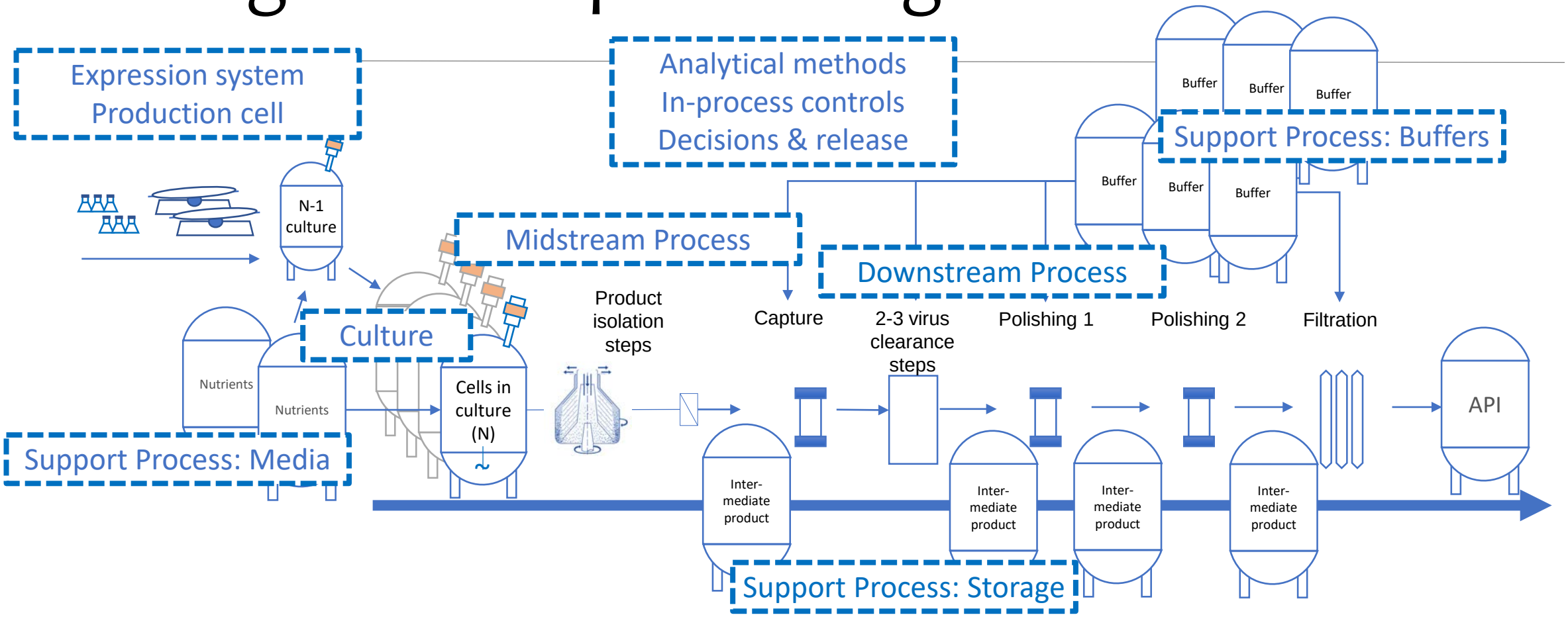
N-bioreactor & before:
- up with output
- down with time

Post N-bioreactor:
- up with yield
- match processing time

Integration of all steps & operations

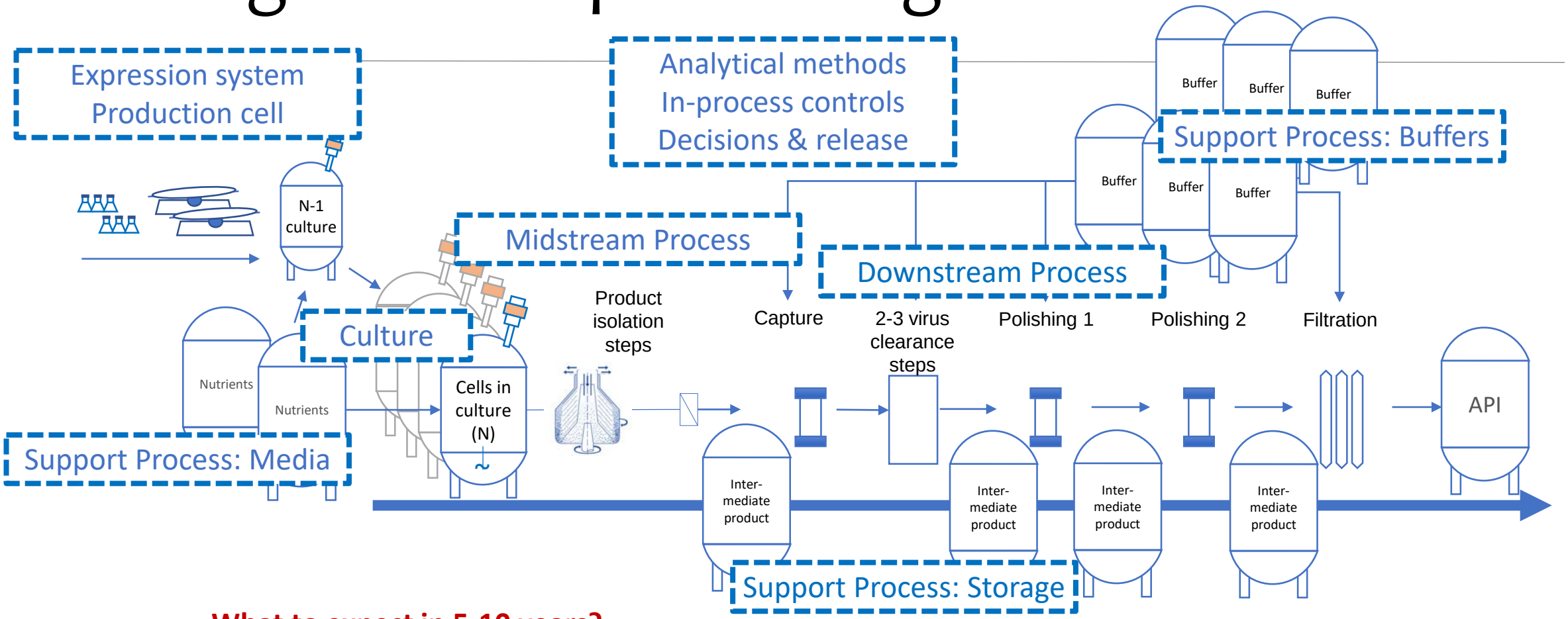
Simplification of the installations

Integrated Bioprocessing Overview



Most process steps can be operated either in batch or continuous mode.
Most equipment is available either in single-use or stainless steel.

Integrated Bioprocessing Overview



What to expect in 5-10 years?

Various modes of continuous operation are introduced but batch coexists.
Single-use installations have grown stronger than stainless but stainless coexists.

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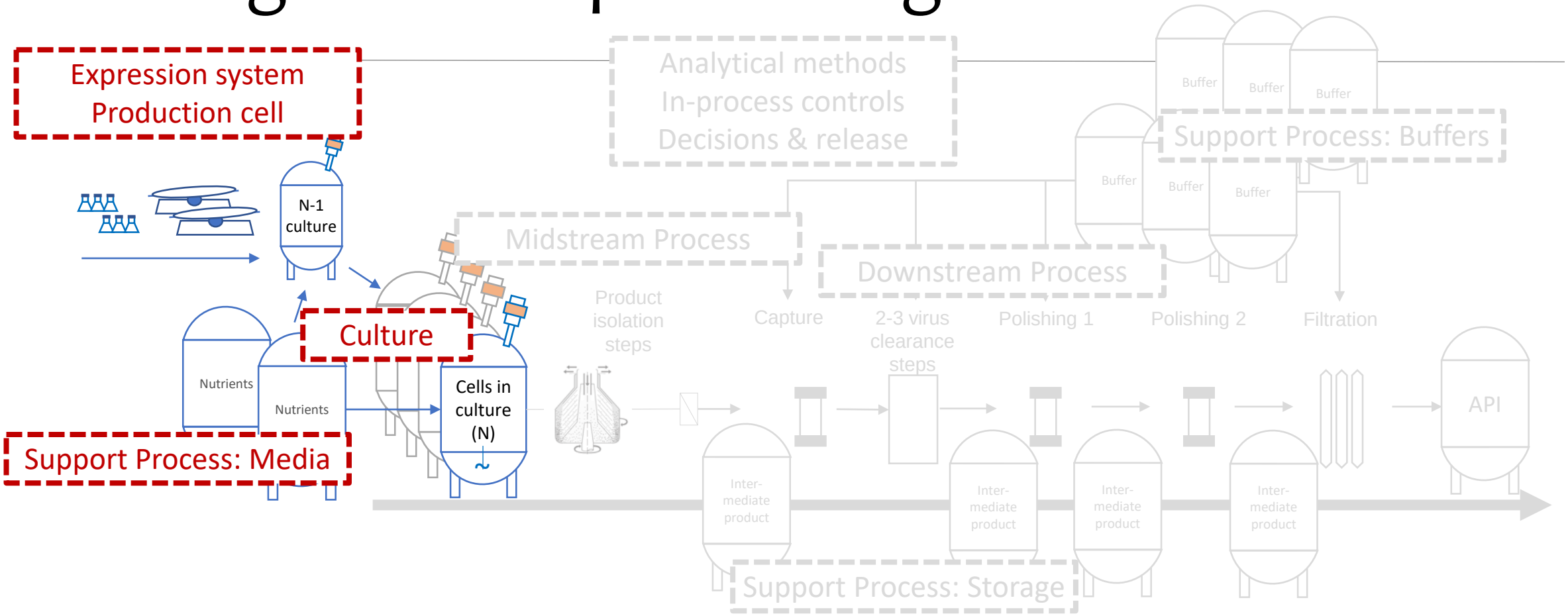

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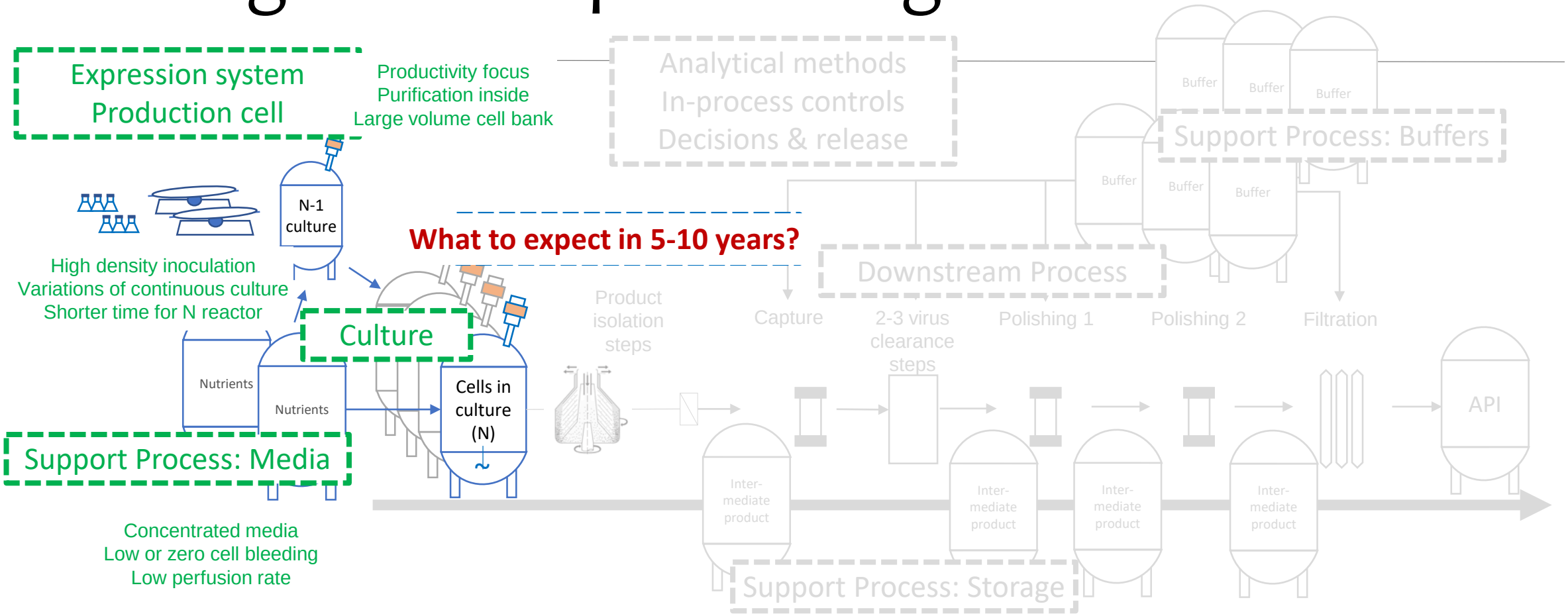

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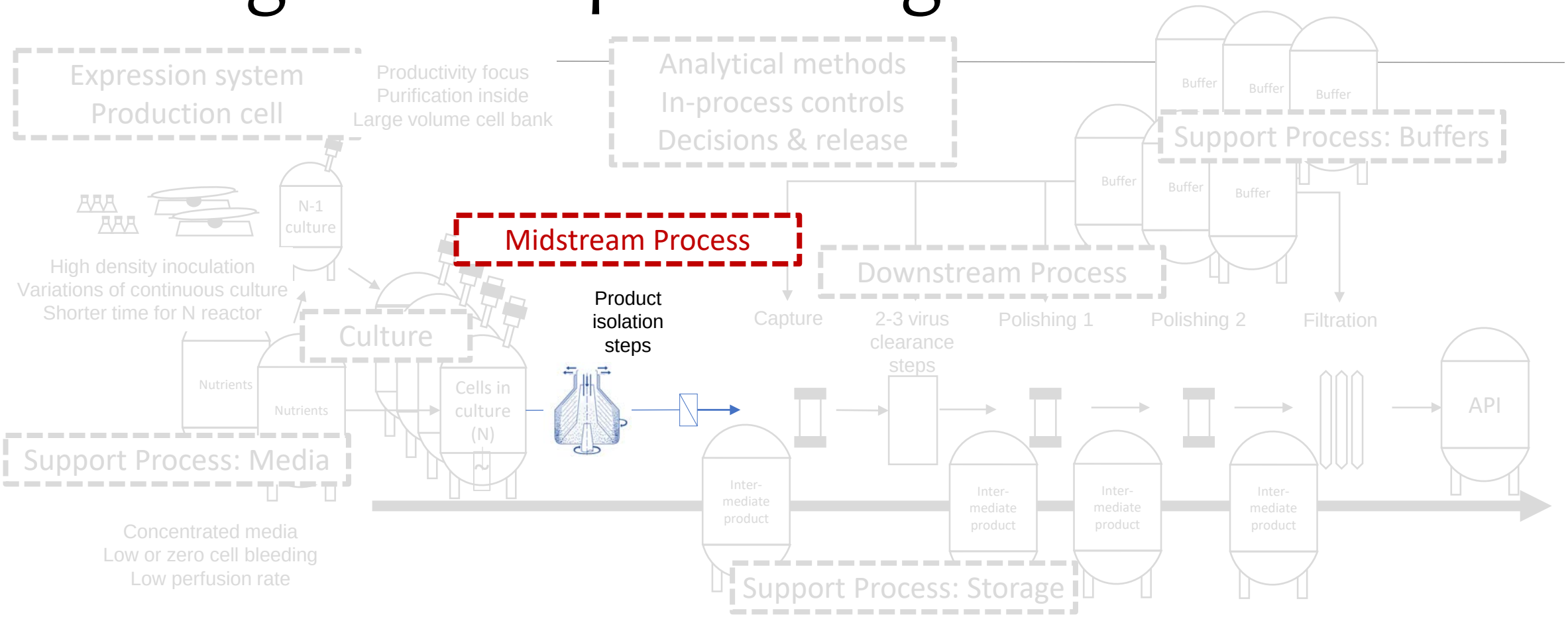

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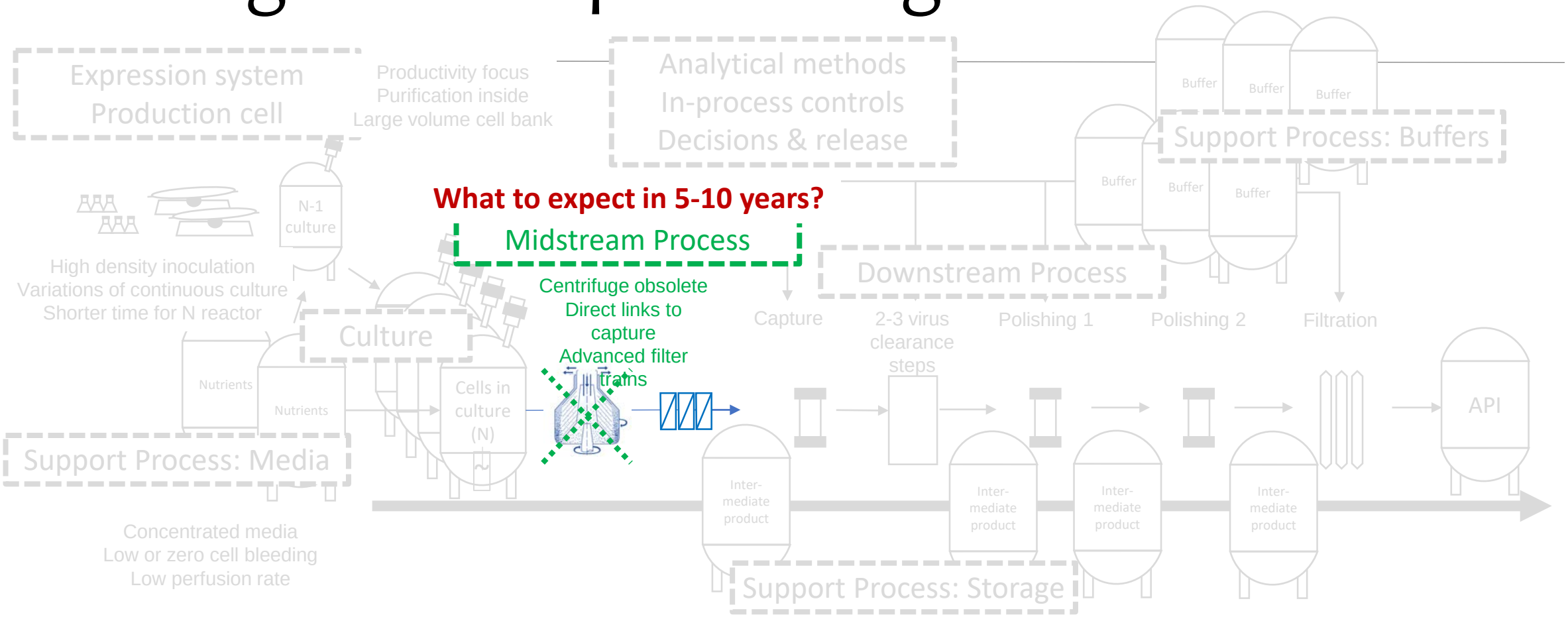

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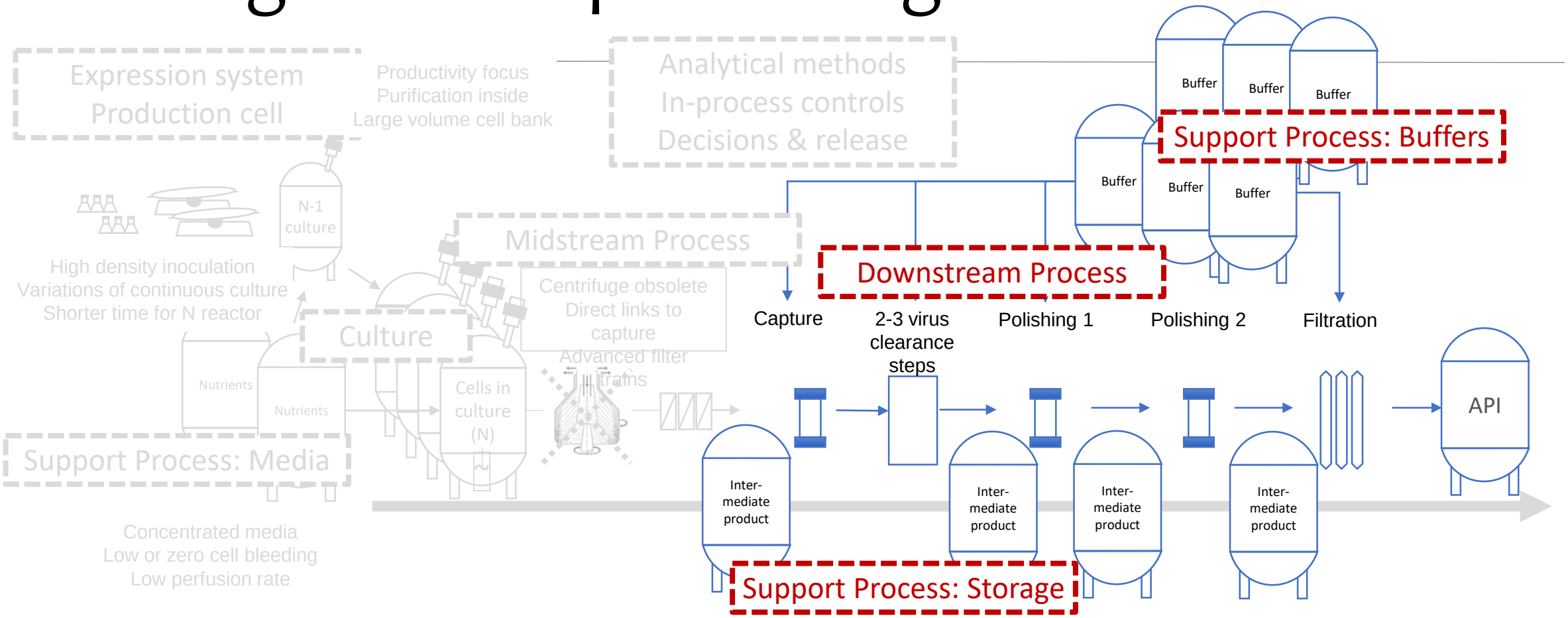

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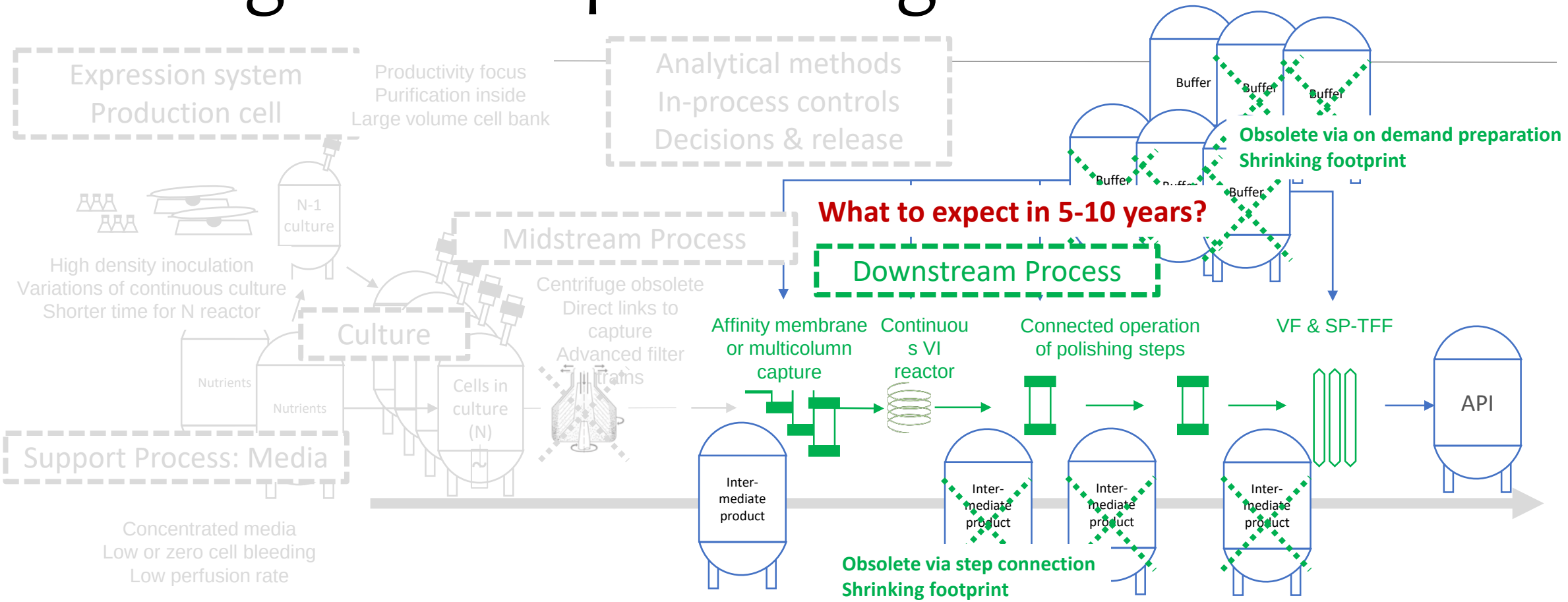

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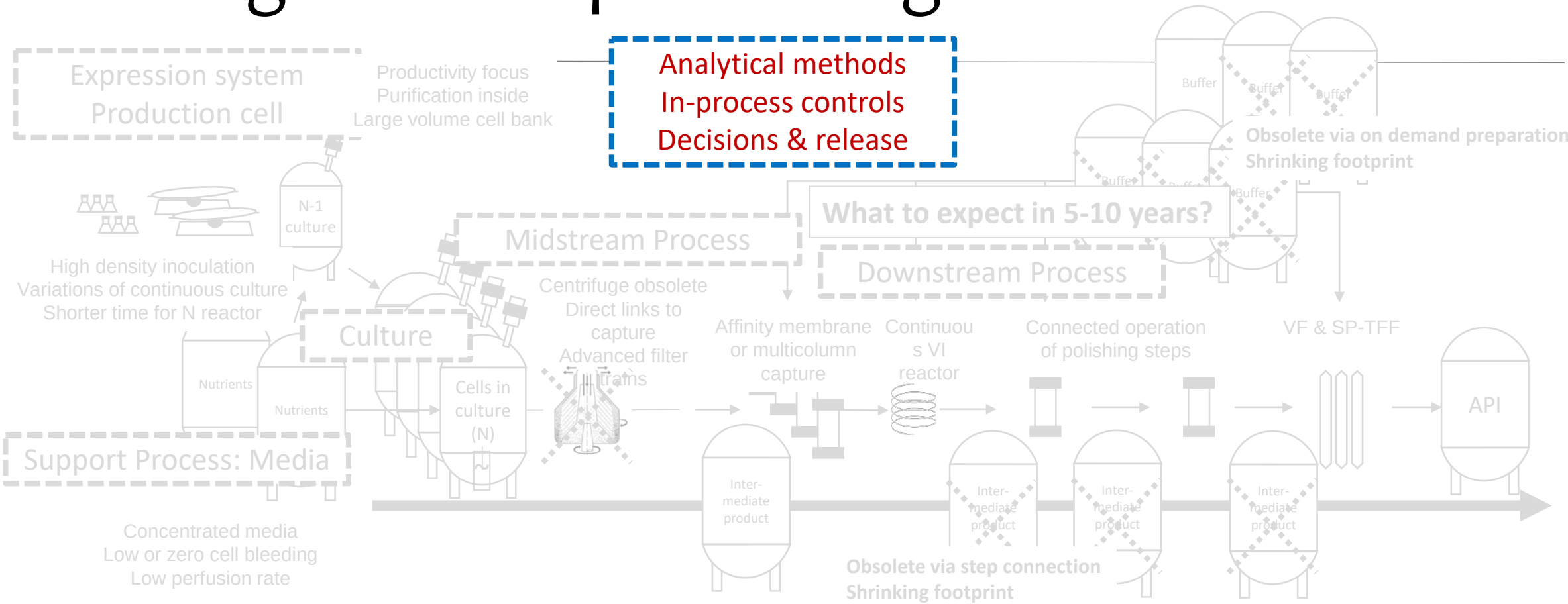

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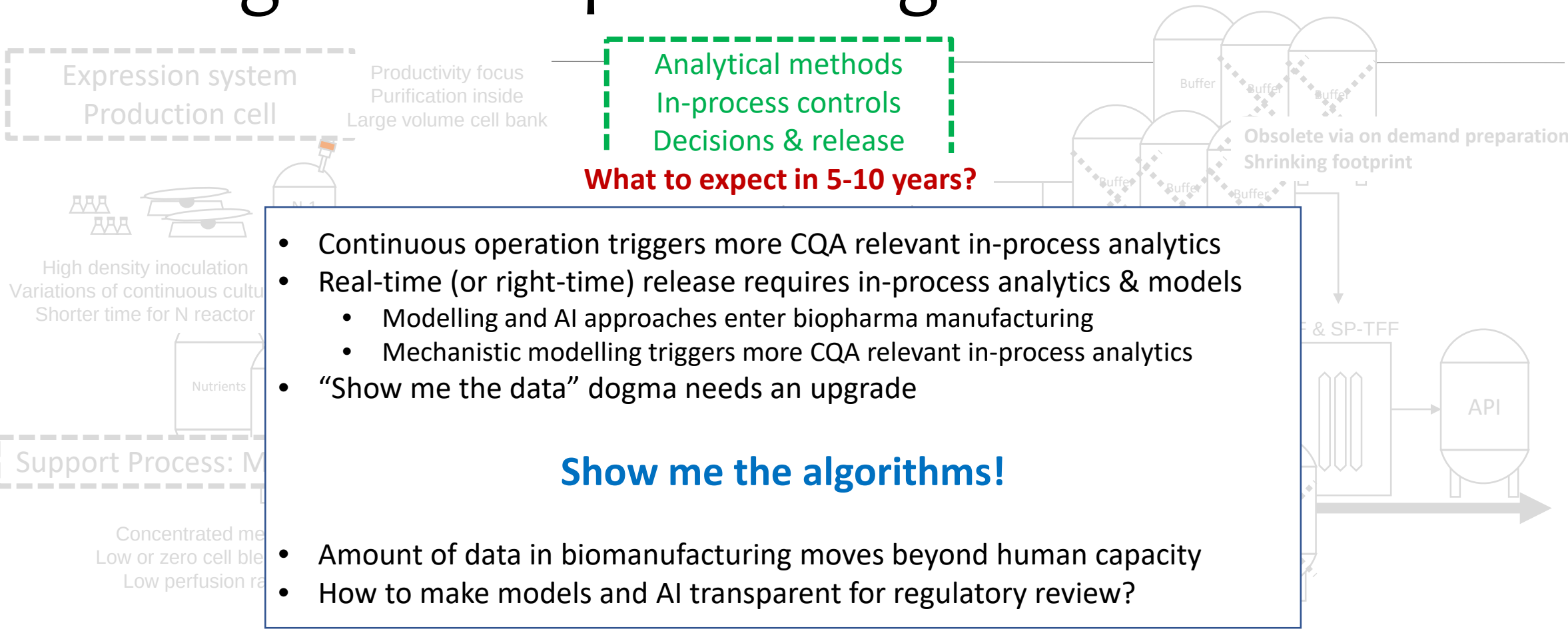

What to expect in 5-10 years?

- Continuous operation triggers more CQA relevant in-process analytics
- Real-time (or right-time) release requires in-process analytics & models
  - Modelling and AI approaches enter biopharma manufacturing
  - Mechanistic modelling triggers more CQA relevant in-process analytics
- "Show me the data" dogma needs an upgrade

Show me the algorithms!

- Amount of data in biomanufacturing moves beyond human capacity
- How to make models and AI transparent for regulatory review?

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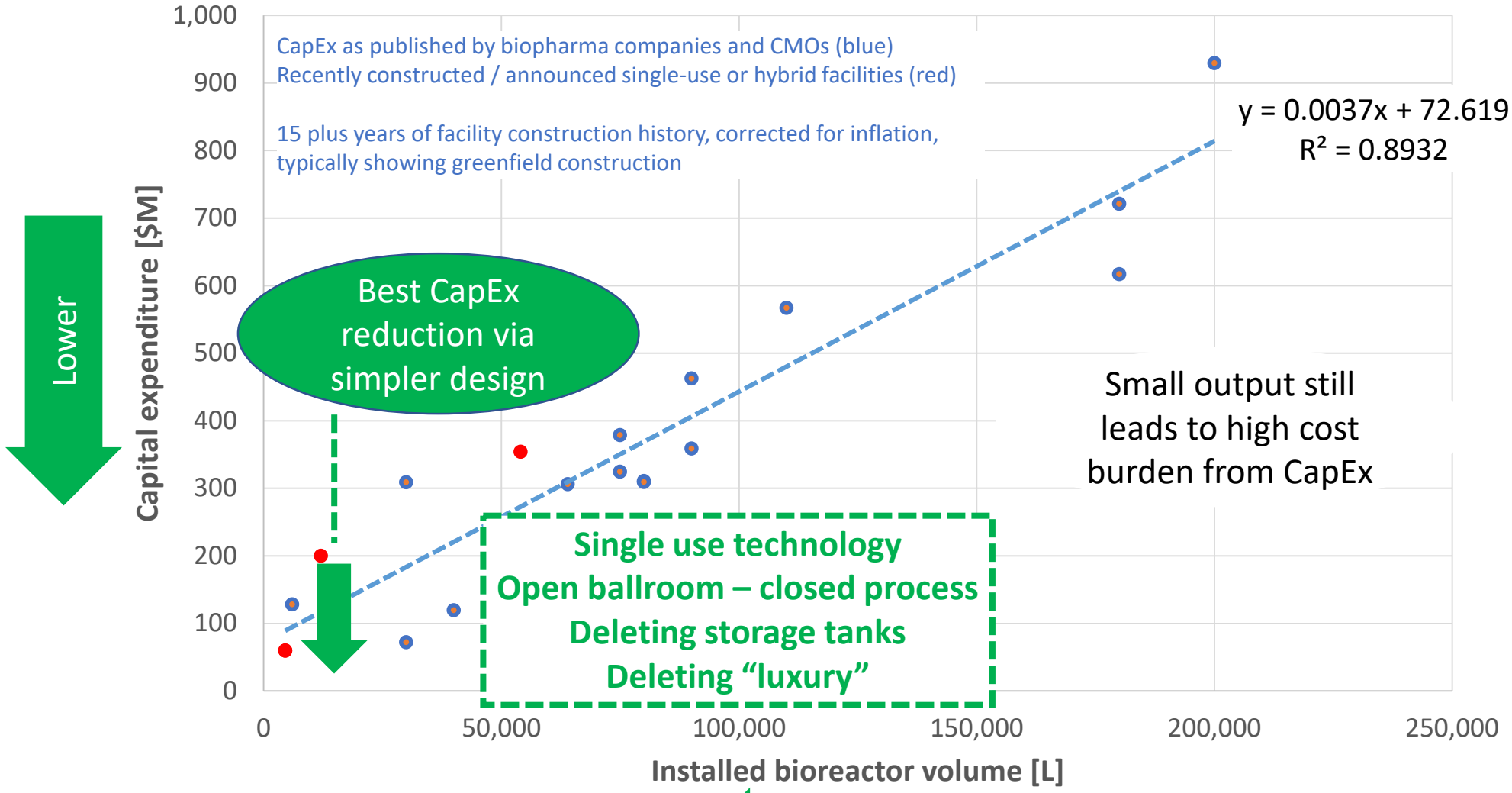
With permission: G Jagschies et al., "Biopharmaceutical Processing": Development, Design, and Implementation of Manufacturing Processes, Elsevier 2018 (graph updated)

Smaller scale - main CapEx reduction driver



Scale reduction – what will you see?

- More single-use technology with advanced control features
- Plug & Play unit operations in modular facilities
- Benchtop scale operation for many small-market therapeutics
- Closed processing for hygienic operation at (very) small scale
- Storage as a support operation disappears

- Inexperienced manufacturers consider manufacturing facilities

Process technology, what will you see?

- Progress with batch mode cell culture up to 10-15 g/L of mAbs
- Continuous mode productivity up to 60-80 g/L for mAbs
- Need to understand CQA effects of high productivity operations

- Affinity membrane-based capture of a reactor within 24 hrs
- In-process prep of buffers first fully algorithm driven operation
- Downstream methods for new impurity profiles, or lower yield
- CQA relevant monitoring & control in fast & continuous processes

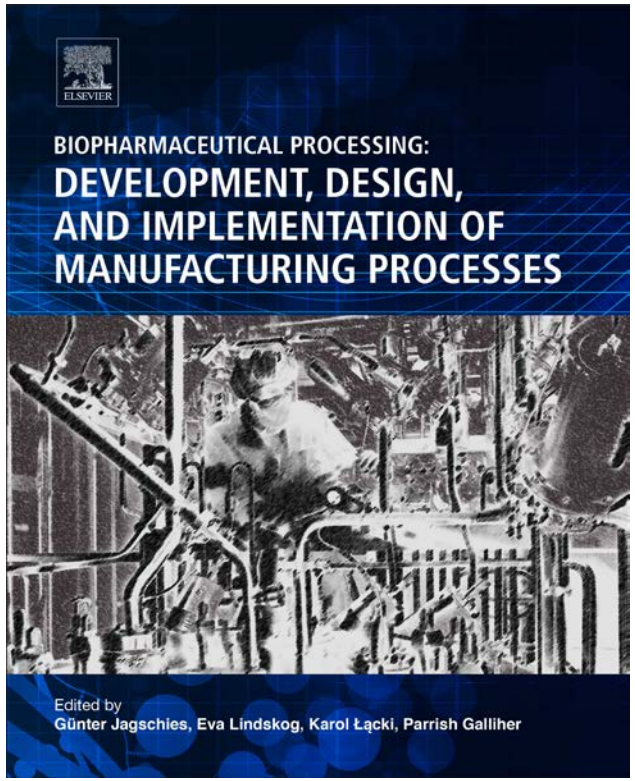
Top ranking improvements – technical

- Controlling the impurity profile produced by cells in culture (a significant process yield issue)
  - Avoid impurities that are hard and expensive to deal with further downstream in the process (many product related impurities)
  - Purification technology that successfully removes very difficult impurities incl. aggregates and isoforms (second best for yield issue)
- Downstream technology matching top productivities from the bioreactor(s)
- CQA relevant in-process monitoring and control technology
- Managing big data in biomanufacturing, refining it for decisions

Top ranking improvements - economic

- Increase of facility productivity
  - High cell density loading of N-reactor (30% increase)
  - Ultra-high batch titers of 10-15 g/L (2-3x increase)
  - Continuous culture with “titers” equivalent to 50-60 g/L (≤ 10x increase)
  - Affinity membrane capture in <24 hrs (2x vs any column process)
- Reduction of facility size
  - Productivity increase x-fold as above enables y-fold lower process volumes and z-fold lower footprint (x > y > z)
  - Deletion of most storage tanks reduces footprint by significant double-digit percentage (e.g., 60% in buffer prep area)

Biomanufacturing Reference



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58 chapters covering

- ✓Disease priorities
- ✓Biopharma business
- ✓Process capabilities & designs
- ✓Principles & Methods
- ✓Equipment & Facilities
- ✓Analytics, Quality, CMC
- ✓Industry case studies
- ✓Economics of bioprocessing

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