Enabling a Healthier World

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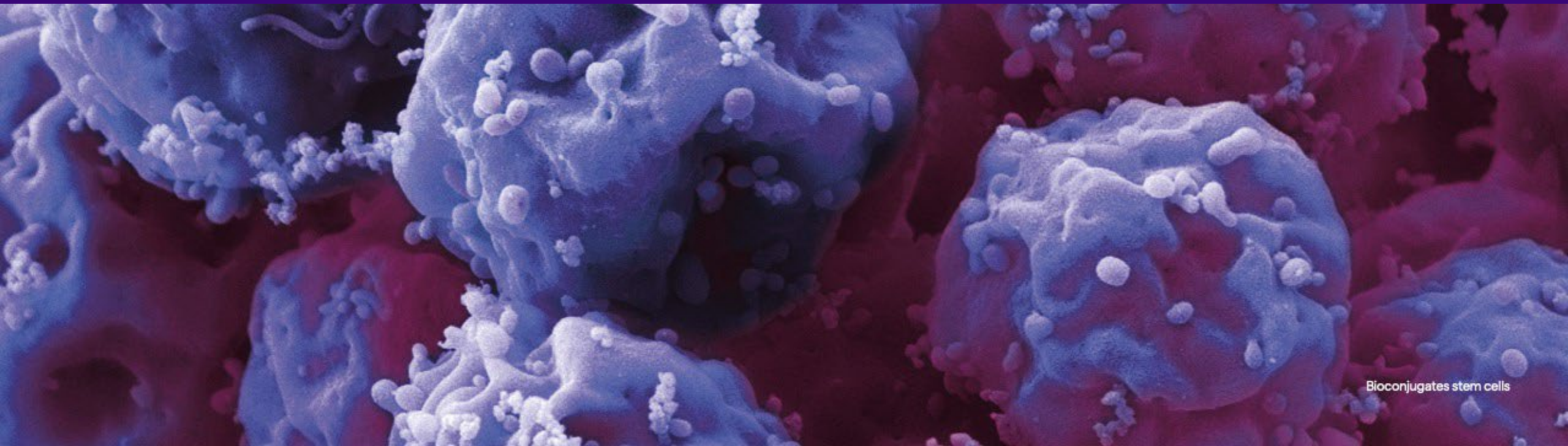
Distributed and Point of Care Manufacturing

Ensuring the Quality of Autologous Cell Therapy Products

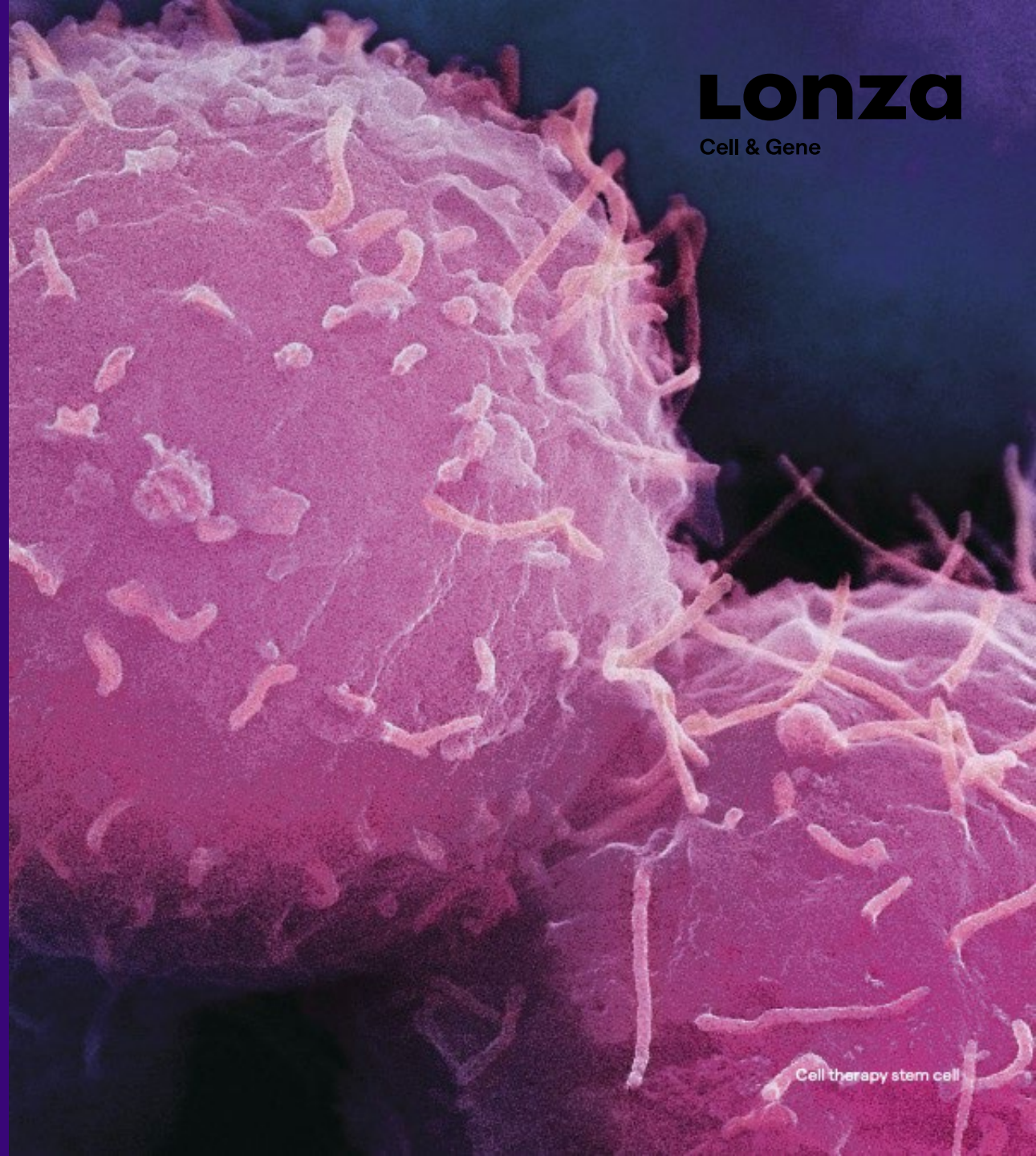
16 November 2022

CONFIDENTIAL



Agenda

- Product/Process Complexity
- Why DM/POC Manufacturing?
- Autologous Cell Therapy Considerations & Challenges
- Industry Needs



Cell and Gene Therapy Manufacturing

Another Scale of Complexity

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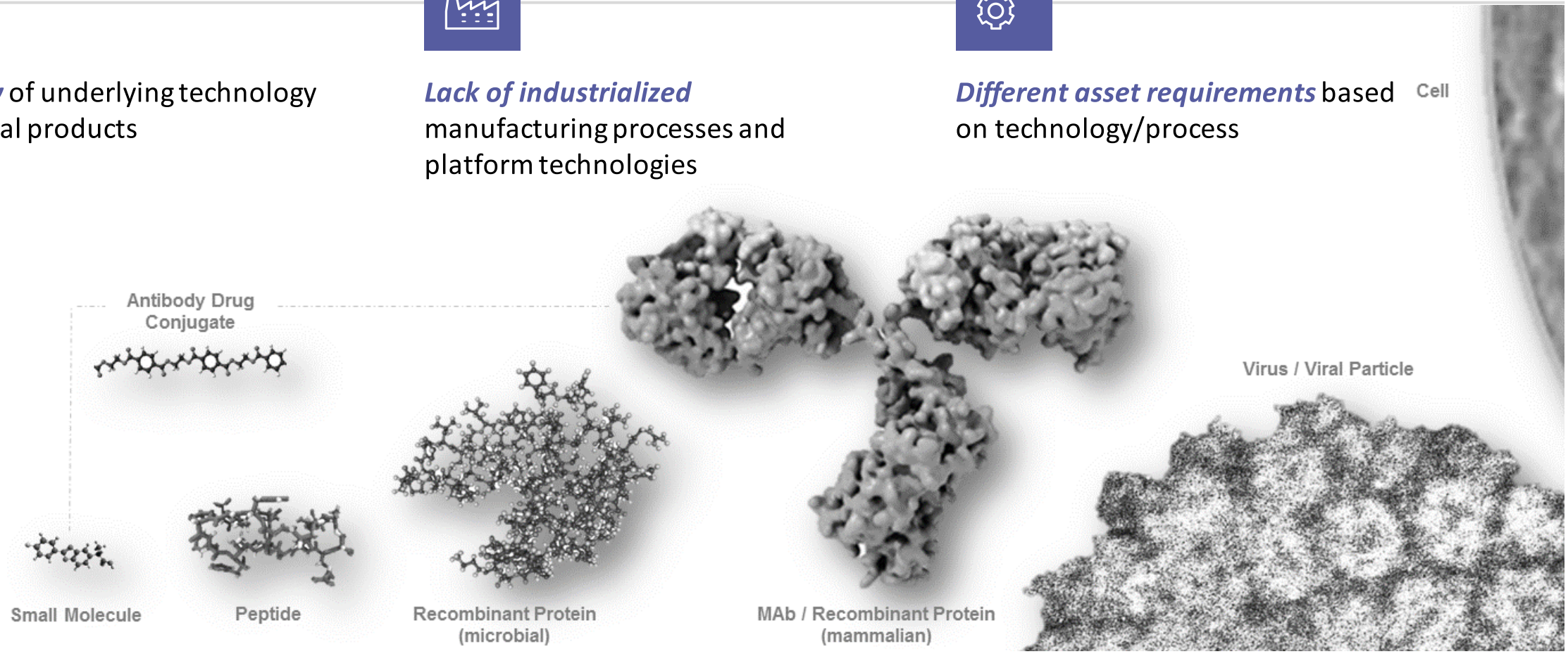
Diversity of underlying technology and actual products

Lack of industrialized manufacturing processes and platform technologies

Different asset requirements based on technology/process



Cell and Gene Therapies

Primary Modalities

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Viral vector manufacturing

- Viruses are used as **"vehicles"**
- **"Off-the-shelf"** model
- **Centralized** manufacturing
- To modify cells **outside or inside body** (ex vivo, in vivo)

Allogeneic cell manufacturing

- **"Off-the-shelf"** model
- **Potential for one donor to treat multiple patients**
- **Centralized** manufacturing

Autologous cell manufacturing

- **1 patient = 1 product**
- **Inherent Variability** in patient starting material
- **Complexity** of manufacturing logistics
- **Limited patient material** increases impact of batch failure
- Strong **efficacy** results
- **Centralized or Distributed** Manufacturing

Needs and Challenges are different by segment

Autologous Cell Therapies

Challenges & Considerations

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Aseptic Processing and Process Simulation - long manufacturing periods in which sterility must be maintained – **no sterile filtration possible** along product pathway

Comparability – challenging due to inherent variability in patient starting material and small batch sizes

Smaller batch sizes - challenges in application of existing guidance around for example visual inspection, reference/retention samples, sterility samples

Processes often require large numbers of manual manipulations (potential aseptic risk), and very long process days meaning high number of operators must be available → strong focus on **training**

Analytical test methods often difficult to qualify to meet right parameters, **long lead times** for execution, selection of right potency assay and link to clinical benefit

Short shelf life of "fresh" product - challenges in batch release process - all critical data available at the time of disposition (release for infusion vs. final release)

Why Distributed Manufacturing?

Proximity to Patients Matters

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Distributed Manufacturing provides a means of reducing vein-to-vein times and streamlining complex supply chain logistics

- Shipment from the hospital to a centralized manufacturing site adds significant complexity
  - Multiple freeze/thaw cycles
  - Complicated transport logistics (both to and from the central manufacturing facility)
  - Scheduling constraints at central manufacturing facility
  - Chain of identity/chain of custody tracking
- For autologous cell therapies, shortening the time between starting material collection and patient dosing leads to improved outcomes (↓ likelihood of disease progression and reduced mortality)
- Potential to prioritize manufacture according to patient medical need due to enhanced connection between treating physician and manufacturing

Traditional Manufacturing

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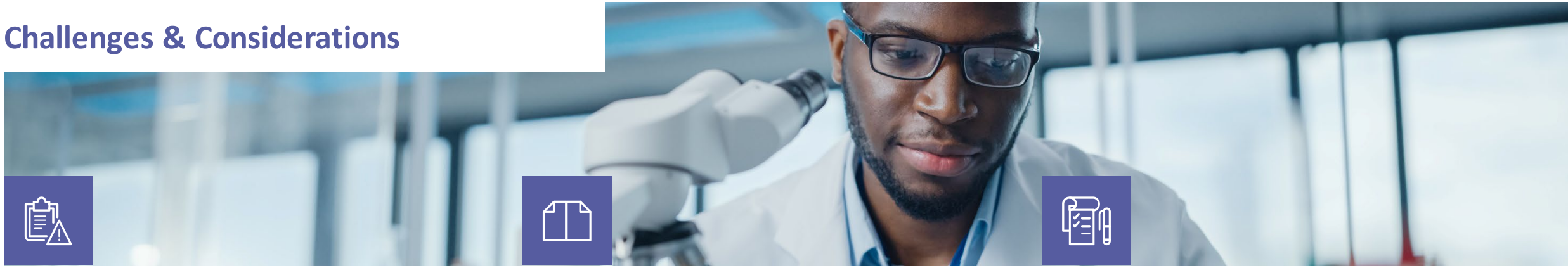
Challenges & Considerations



Accelerated clinical development means compressed timelines for CMC activities → phase appropriate GMPs

Segregation and Prevention of Cross Contamination: facility and HVAC design, disinfection studies including microorganisms and viruses, etc.

Ensuring the sterility of cell therapies necessitates end to end aseptic processing

- Cell therapies (and also some viral vectors) are unable to be sterile filtered resulting in the need to utilize sterile reagents, consumables
- Routine aseptic process simulations are required to demonstrate operator performance and effectiveness of process controls

Complex biological starting materials, partially highly variable, sometimes only available from a single source, not always of adequate quality/grade to support GMP manufacturing

Raw materials often novel, not always of an adequate grade to support GMP manufacturing, and potentially difficult to source

Point-of-Care Manufacturing

Challenges & Considerations

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Point-of-Care settings often lack the appropriate infrastructure, policies, and procedures to operate as a drug manufacturer

- Lack of a qualified cleanroom environment and supporting utilities
  - Open manipulation of product and ancillary materials requires access to a Class A/B environment
  - Alternate solutions include use of automated, functionally closed systems offering end-to-end manufacturing capabilities
- Deficient or non-existent Pharmaceutical Quality System (PQS)
  - Healthcare Facilities not in the business of manufacturing drug product would not have established quality management structure, policies, and procedures in place
  - Potential for application of a control site strategy (hub and spoke model) with responsibility for PQS establishment
- Supply chain practices not aligned to cGMP
  - Ordering, receipt, inspection, and testing of cGMP raw materials
  - Kitting could be performed at a central site; however, some form of inspection would be required upon receipt

Point-of-Care Manufacturing

Challenges & Considerations

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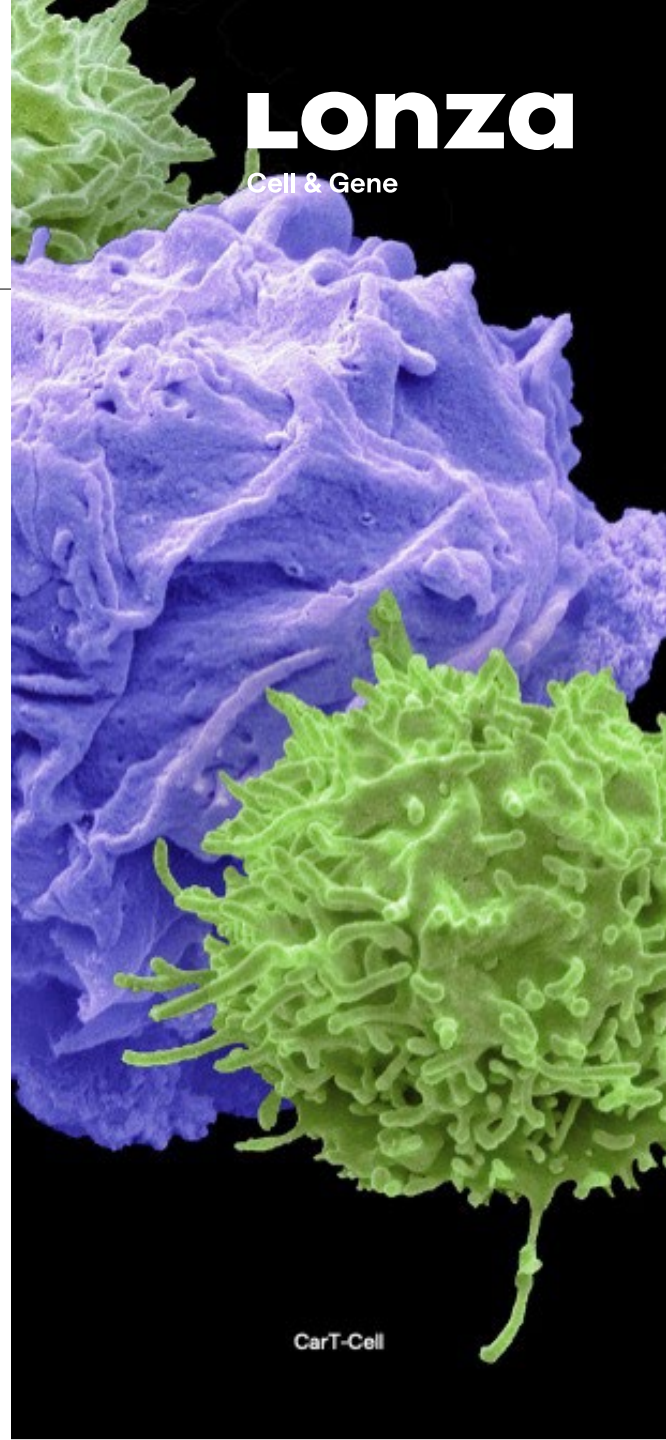
Point-of-Care settings often lack the appropriate infrastructure, policies, and procedures to operate as a drug manufacturer

- Personnel constraints
  - Additional training requirements for personnel conducting cGMP operations
  - Need for clear segregation of duties, roles, responsibilities, and decision-making between clinical and manufacturing activities
- Lack of access to appropriate Quality Control laboratories for raw material, in-process, and finished product testing
  - In-process results are often needed real-time requiring close-proximity to laboratories and on-call staff to execute testing
  - A hybrid approach to testing could reduce the amount of equipment and personnel required at point-of-care
    - Tests for results required real-time (in-process or release) would be performed on-site and the remainder at a central laboratory

Analytical Methods

Analytical Challenges & Considerations for Autologous Cell Therapies in a Point-of-Care Setting

- Smaller batch sizes for some autologous therapies limit the amount of in-process and release testing that can be performed
- Short shelf life of products combined with the small batch sizes pose a challenge for collection of stability data
- Complex cell-based test methods are often difficult to qualify and have long lead times for execution
- Availability of lab equipment and trained personnel for testing in point-of-care facilities may be limited; therefore, consideration should be given to where testing should be performed
  - Central lab, at POC, or Hybrid approach
- If adopting a decentralized approach, assay transfer requirements and appropriate controls will need to be clearly defined



Real-Time Release

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Solutions for real-time release are needed to address the short shelf life of some "fresh" autologous products

- Data normally considered critical for disposition decision may not be available (Pharmacopoeia sterility, USP Mycoplasma, Environmental Monitoring) prior to the need for patient infusion
  - A release for infusion followed by full product disposition may be required
  - A formal plan must be in place detailing what testing is required prior to infusion and actions in response to any positive sterility or mycoplasma test results or failing long lead time test
    - The plan should include communication to treating physician for any possible required interventions
- A robust real-time release can be achieved by applying quality-by-design principles in process development and making use of available rapid analytics
  - Leveraging real time analysis (in-line or offline) of critical quality attributes and process parameters over extensive end of line testing

Comparability

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Traditional approaches to demonstration of comparability may not be applicable to autologous cell therapies manufactured at point-of-care

- Direct site-to-site comparison not logistically feasible for a large number of POC sites
  - Limited patient (or healthy donor) starting material renders split apheresis approach unfeasible
  - Small patient populations in early phase trials and inherent donor to donor variability limits available and relevance of legacy data for comparison
- A risk-based approach dependent on the level of standardization across POC sites is recommended
- In a hub and spoke model, comparison to the Central Site (Hub) versus across POC sites may be performed as part of formal technology transfer
- Dependent on the level of complexity for DM units, the addition of new DMs to a previously approved POC site could be based upon the principles of standard cGMP requirements for equipment on-boarding and qualification

Where do we go from here?

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Industry Needs

Analytical Methods

- Need for development of in-line analytics and rapid release methods
- Use of alternative sampling schemes for high volume methods
- Elimination of AO material usage to reduce the need for long lead time adventitious agent testing
- Identification of surrogate markers for assessment of potency

Adoption of available technology platforms

- Closed, automated manufacturing platforms
- Remote monitoring tools
- Integrated/all-in-one software (eBRs, LIMS, COI/COC tracking, Quality Record Management)

Guidance from Regulators

- Global harmonization on definitions and approach to regulation
- Expanded guidance on expectations for parametric release of ATMPs
- Guidance on the approach to facility registration and inspection for POC manufacturing with a centralized PQS
- Clarification on how to define and qualify a DM Unit

Thank You

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