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THE WESTIN BOSTON SEAPORT DISTRICT - BOSTON, MA

Manufacturing Therapies with Complex Modalities: Seamless Integration from Development Through Commercial Scale-Up

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AGENDA

- Introduction
- Case Study 1: Monoclonal Antibody (Scale-up)
- Case Study 2: Radioligand Therapy (Scale-out)
- Preparing for Regulatory Interaction
- Efficiency through Digitization
- Conclusions

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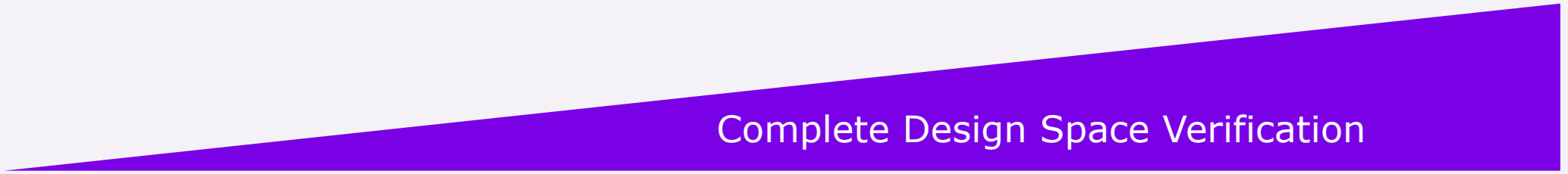
01 Introduction

EVOLUTIONARY CONTINUUM OF DRUG DEVELOPMENT

Process knowledge evolution through development lifecycle

Evolutionary Steps	• Initial QTPP • Define CQA • Establish Preliminary Control Strategy	• IND • Refine CPPs • Strengthen Analytical methods • Supply clinical trials	• Expand process characterization • Validate critical analytical methods • Finalize formulation and delivery	• Commercial Scale • Validate analytical methods and finalize specifications • Finalize Process Control Strategy • Validate process • BLA/NDA	• Post-Approval Changes • Continued Process Verification
Development Stages	Tox Studies	Phase I	Phase II	Phase III	Post-Approval



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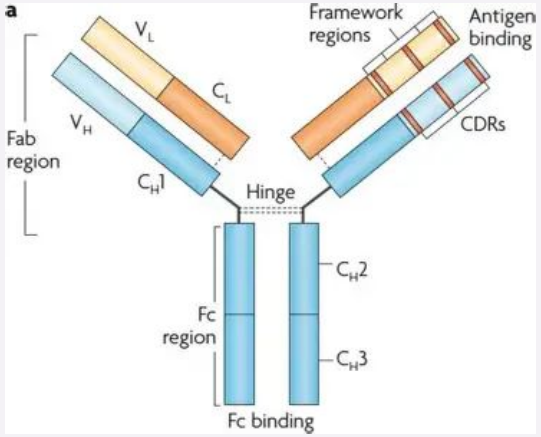
Case Study 1 (Scale-Up)

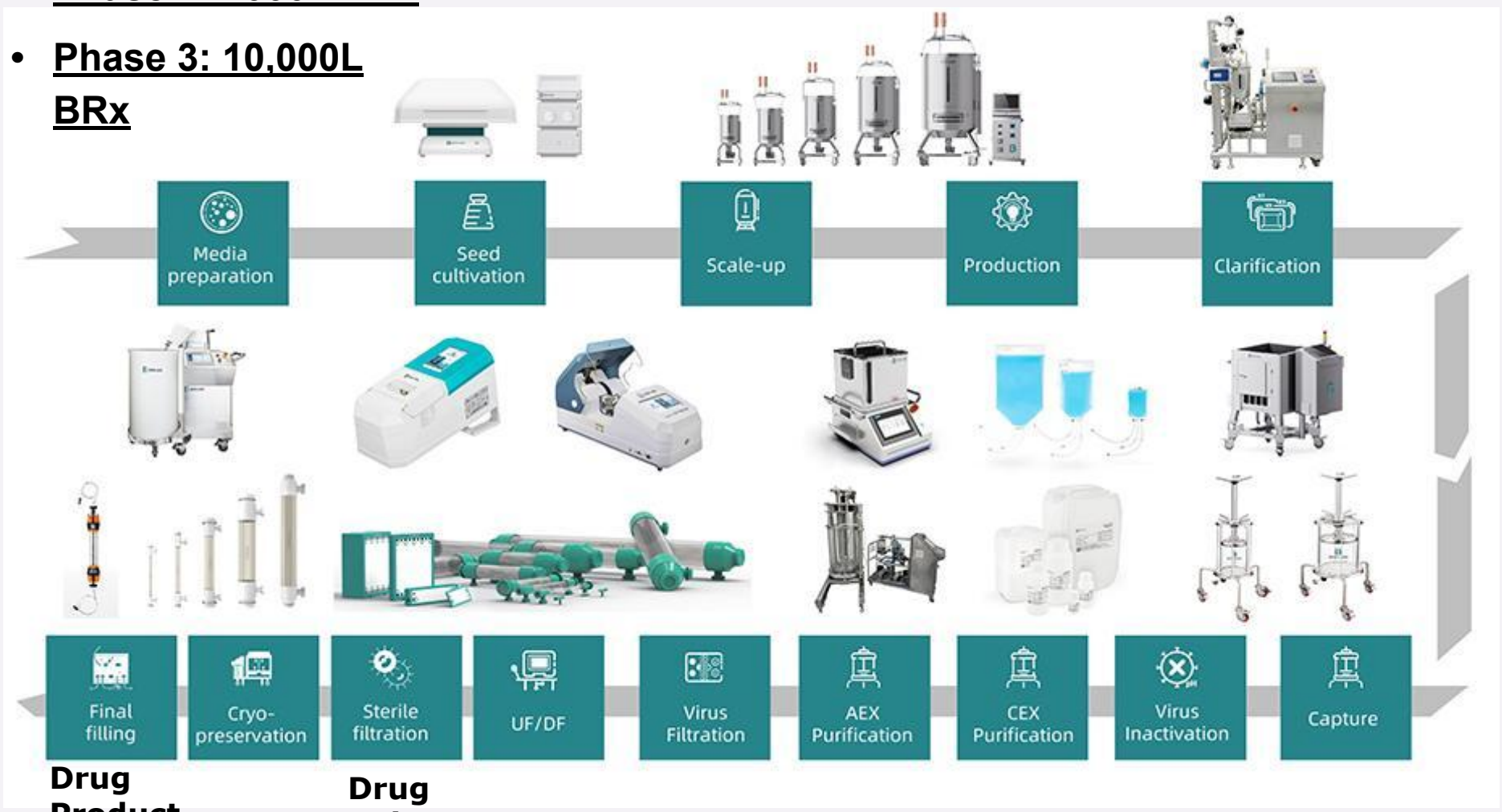
SCALE-UP AND CHARACTERIZATION OF A MONOCLONAL ANTIBODY

How do you manufacture Monoclonal Antibodies?



- IgG1 mAb produced from recombinant Chinese Hamster Ovarian cell line
- A mechanism of action is by Antibody-Dependent Cellular Cytotoxicity

- **Phase 1: 1000L BRx**
- **Phase 3: 10,000L BRx**



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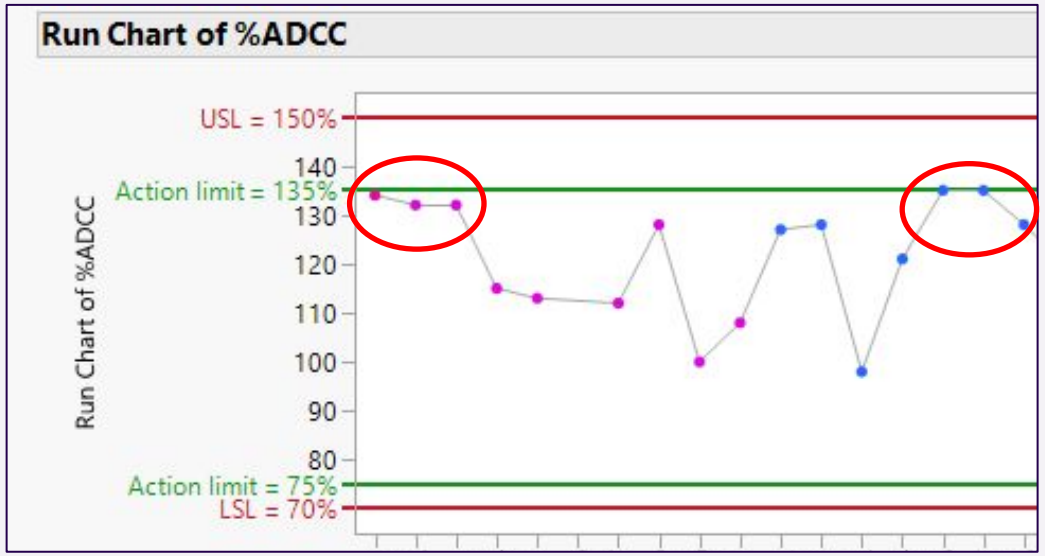
Why was the Antibody-Dependent Cellular Cytoxicity (ADCC) Bioassay drifting high?



- Root Cause High [Mn] in media
- CAPA: Raw material metal testing strategy
- G1F most at risk of being OOS due to Mn impurities in process:
  - ❑ Timing of Mn addition ☐ significant impact on quality (more impact if added in basal media)
  - ❑ Model generated to predict G1F as a function of [Mn] in raw material

Sructure Activity Knowledge

Quality Attribute	Impact on ADCC
Afucosylated species (G0, Man5 and G0-GN)	High
Galactosylated species (G1F and G2F)	High

Literature

Loebrich et al., Comprehensive manipulation of glycosylation profiles across development scales. mAbs. (2019) 11(2):335-349.

Feed Attribute	Quality Attribute
Manganese Level	Increased G1F
Copper Level	Decreased Man5

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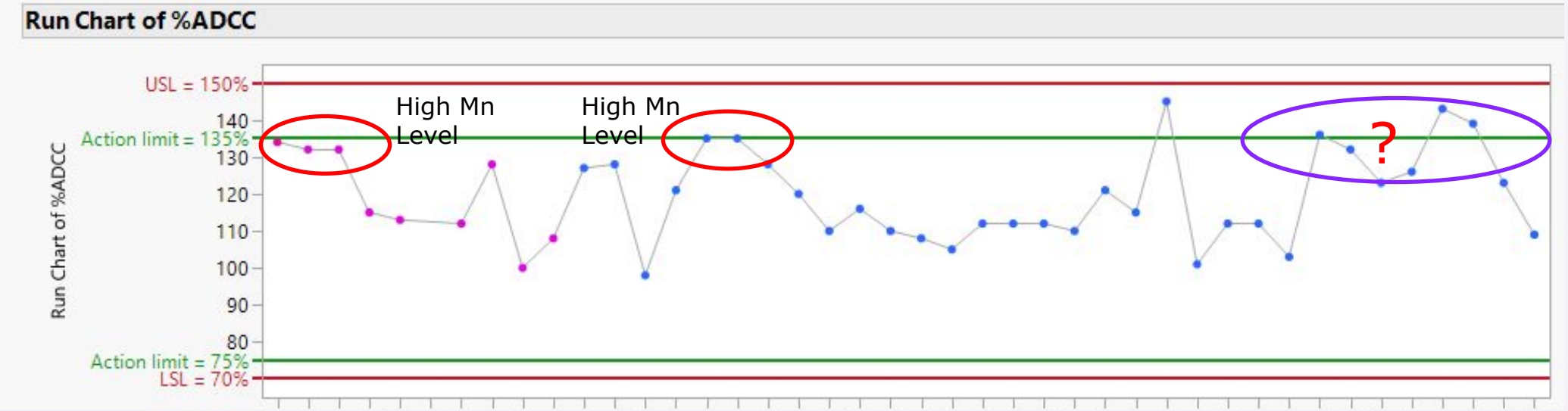
Now what happened?



Feed Attribute	Quality Attribute
Manganese Level	Increased G1F
Copper Level	Decreased Man5

Copper Level in Feed was too low

Immediate CAPA: **Set interim low copper limit**
Mid-term CAPAs: **Review metal control strategy** based on statistical multivariate analysis

Lessons:

1. Design space verification occurs well after PPQ
2. Scientifically investigate out of trends
3. CAPAs should be wholistic

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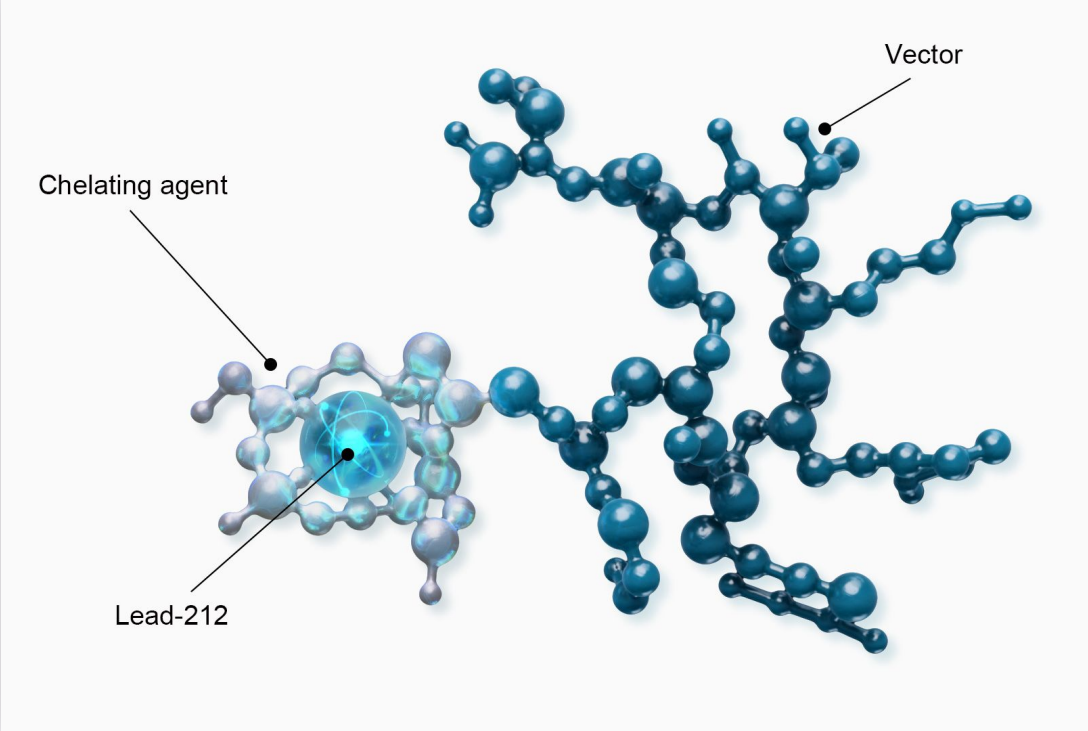
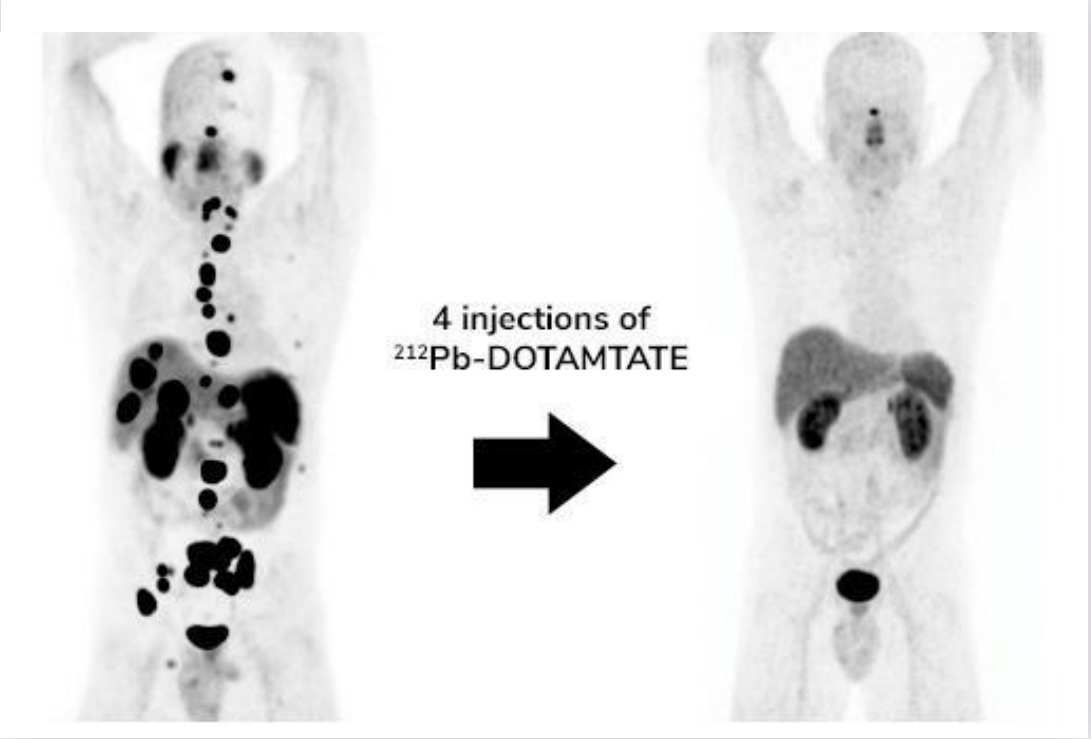
03 Case Study 2 (Scale-Out)

BUILDING SPEED OF DELIVERY: RADIOLIGAND THERAPY

Radioligand Therapy





Volume-rendered images of ^{68}Ga-DOTATATE PET/CT scans from patient MAD4-02 before treatment with 4 cycles of 212Pb-DOTAMTATE at dose of 2.50 MBq/kg (67.6 µCi/kg) for each cycle

Journal of Nuclear Medicine 2022 Sep;63(9):1326–1333

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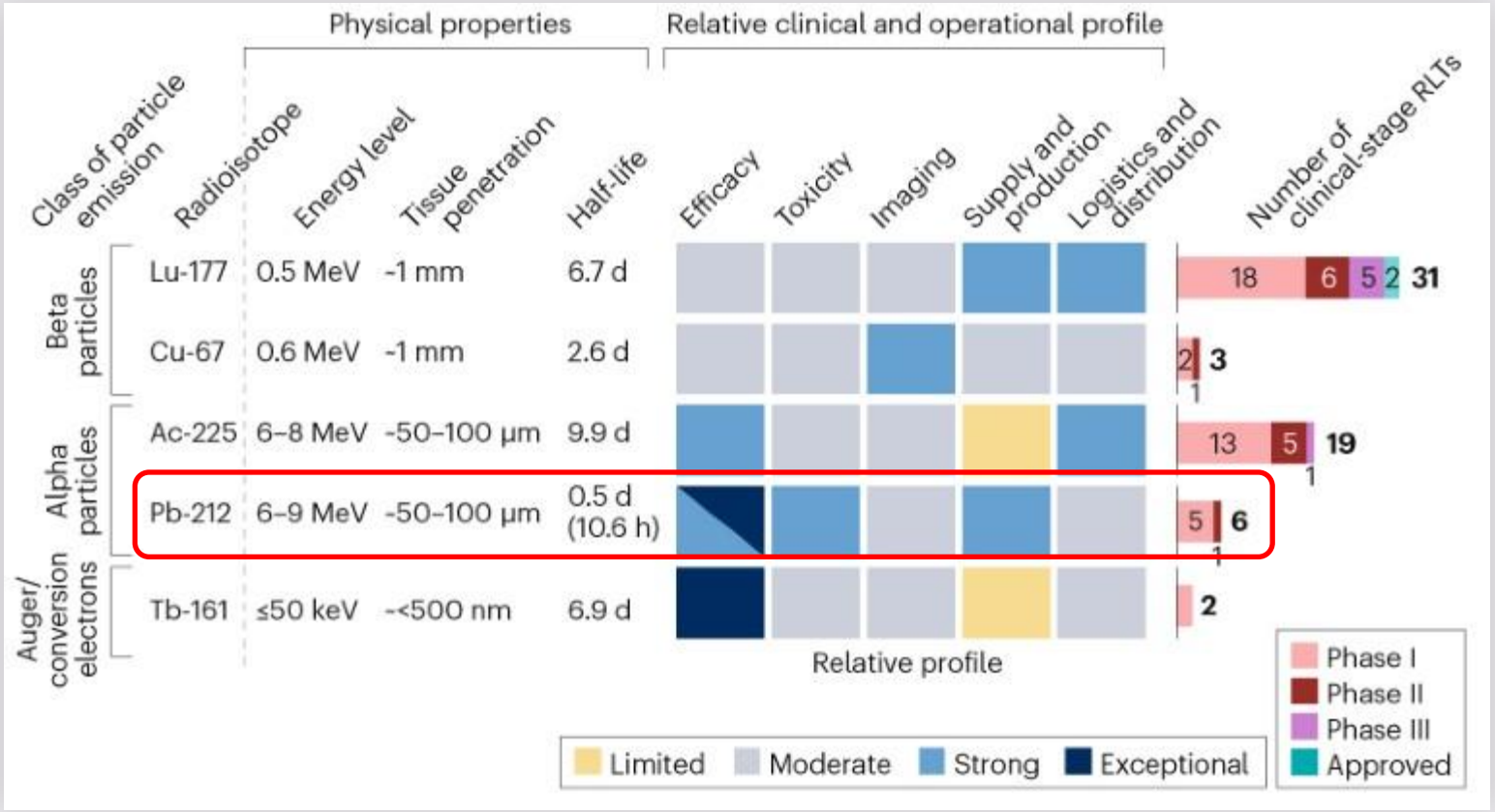
How fast can you get it to the patient?



Nature Reviews Drug Discovery Volume 24 | 03 June 2025 | 584–585 | Jerrick To *et al*

Challenges

- Short half-life requires just in time manufacturing and logistics
- Radioactive Safety
- Aseptic process
- Scale-out not Scale-up increases cost
- High degree of personalization (manufacturing dose maybe dependent on time to patient vein)
- Manufacturing complexity
  - Vector peptide/mAb
  - Linked to Chelating agent
  - Alpha or Beta particle emitting element

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How to test, release, transport and deliver sterile, radioactive drugs in 24hours?

Vector + Chelator **- 1 year**
Radio Pb 212 **- 28 h**

Drug Substance

- **Vector standard pharm production**
- **Radioisotope production is complex**
- **Final step in chemical hot cell**

-24h

Drug Product

- **Precise Demand**
- **Integrated Suite**
- **Fully automated formulation, filling inspection and labeling pharma hot cell**

QC Testing/QA Release **-18h**

Testing & Quality Release

- **Rapid chemical testing, filter integrity testing**
- **Sterility testing post-release**

At hospital**– 4h**

Transport & Delivery

- **Location near hub**
- **Integrate shipping into plant**
- **Radiation dose check before and after delivering to patient**

Lessons Learned

- **Custom equipment (delays in C&Q)**
- **Keep process flows simple for easier scale-out**
- **Talent and resource management key**

Can we translate these efficiencies into other modalities?

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04 Preparing for Regulatory Interaction

FOCUS ON RISK MANAGEMENT AND STORYBOARDS

Why create a White Book: A compilation of position papers

White Book

- **Anticipated questions** from regulatory inspectors and investigators
- **Prepared responses** to these questions
- **Supporting documentation** for these responses

Purpose

A preparation tool for potential regulatory questions

A reference document ensuring consistent responses

A training resource for personnel interacting with inspectors

A risk mitigation strategy for addressing known issues proactively

Sources

- Regulatory questions **generated during development** phases
- **Quality events, Trends** encountered during project development
- **Findings** from previous audits

Outcomes

- **Dynamic** Document
- **Updated** with new data and after information requests
- Use for **training** SMEs

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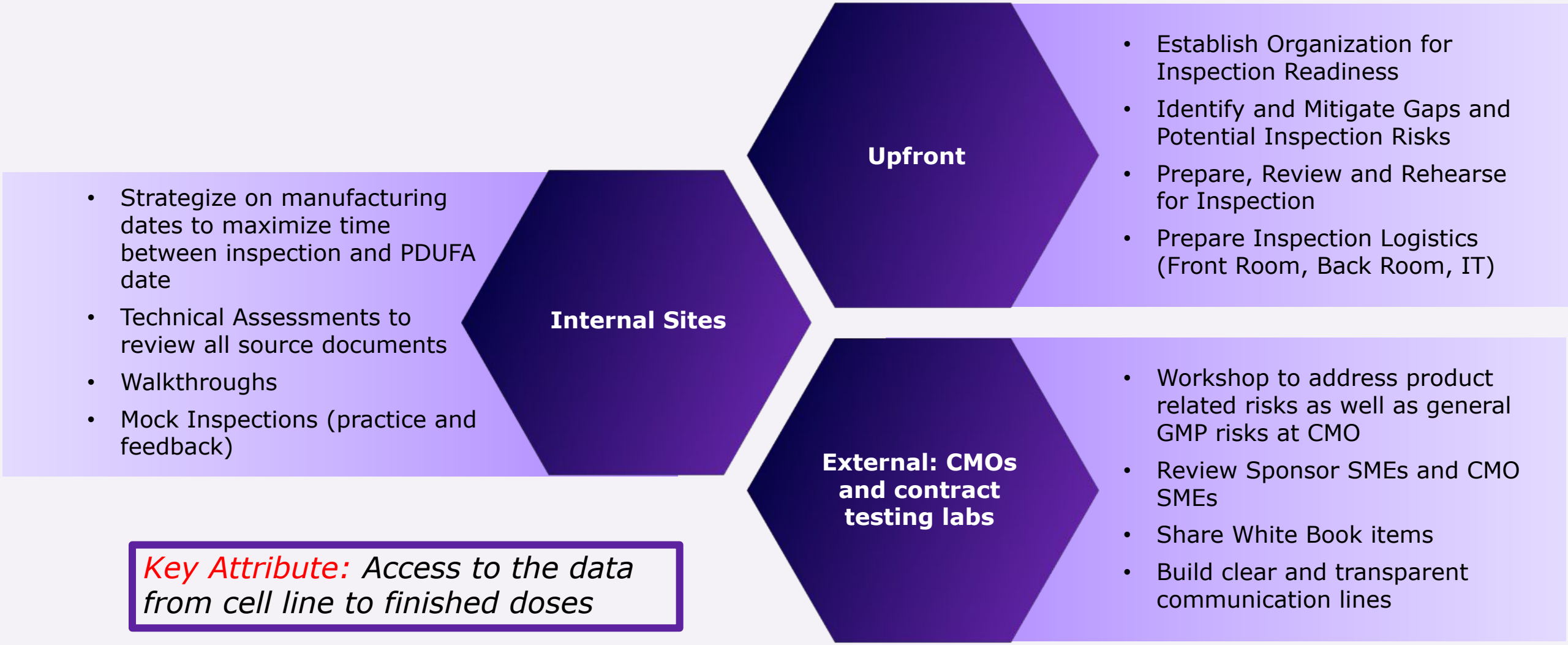
How to prepare for inspections



Key Attribute: Access to the data from cell line to finished doses

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05

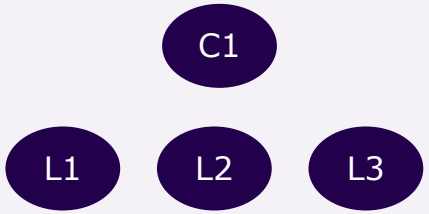
Efficiency through Digitization

COMPILING AND INTEGRATING THE DATA

Why an integrated solution (example of a biologics product)

Internal

Contract



Systems

- 4 manufacturing plants
- 8 testing labs
- Multiple data historians
- 2 LIMS
- 2 SAP systems
- Paper Batch Records (all)
- Paper Testing Records (all)
- Veeva QMS (deviations, change controls, risk management)

Purpose (Data at your fingertips)

1. Data tables and charts for regulatory filings
2. Living, digital repository of all process and testing data including clinical supply lots for invesigations
3. Batch genealogy (which RM, DS, DP went into finished lot)
4. Stability data
5. Process characterization data
6. Query with Gen AI tools

Process of Data Integration

1. Convert paper data to digital(Contract and Internal Paper Records)
2. Connect and contextualize all digital data sources
3. Data Analysis and Visualization Tools
4. Custom Reports
5. Validateable
6. Lives with the lifecycle of the product

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Why an Integrated Solution is so Difficult?

Key Challenges of an Integrated Solution

MODALITY COMPLEXITY

Should work with mAb, RadioLigand, Cell Therapy, Small molecules and other New Therapeutic Modalities

SUPPLY CHAIN COMPLEXITY

Should work seamlessly with a mix on Internal and External Manufacturing including multiple suppliers

SYSTEM COMPLEXITY

Should work with different IT systems and with data captured on Paper

REGULATORY INTERACTION

Ability to provide common processes and standards for regulatory interactions

INTEGRATING WITH EXISTING PROCESSES

Integrated Solution integrate smoothly with existing workflows and systems

COMPLIANCE & SECURITY

GMP Validation, CFR Part 11 Compliance, and Security are essential for a shared platform

Current Workflow across all Challenges

Connect Data

(Silo, System, Signal, Streaming, Social)

Apply Analytics

(AI/ML, natural language processing)

Acquire Insights

(Discover, design, define opportunities)

Point Solutions

(Quality, Manufacturing, Supply Chain…)

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Time taking + Expensive + Difficult to sustain

Knowledge Graph for All Manufacturing Data

Level 04 — Business Planning & Logistics
ERP, QMS, SCM

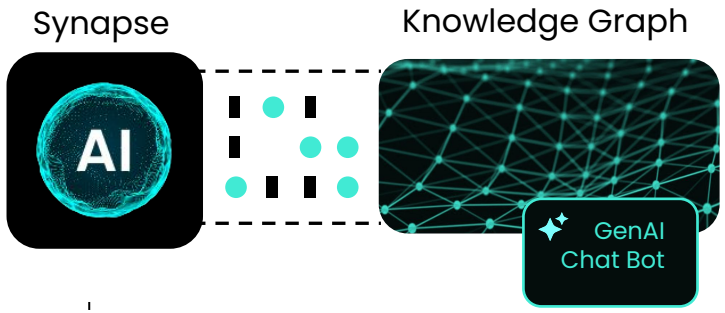
Level 03 — Manufacturing Operations
MES, LIMS, PBR

Level 02 — Monitoring & Supervising
SCADA, PLC< DCS, PID

Level 01 — Physical Equipment
IoT, Sensors, Valves

Knowledge Graph makes Manufacturing data AI ready

Mareana Platform



ML Algorithms & Rules: sort data into nodes and edges

1. Works for all modalities
2. Works with internal and external manufacturing
3. Works with system and paper data
4. CFR Part 11 Compliant and Secure

Outcomes

Supply Chain
- SC Knowledge graph as a data asset
- Ad-hoc analysis and insight generation
- OOB KPIs and Simulations

Commercial Manufacturing
- Continued Process Verification (CPV)
- DPMM Level 5.0 capabilities
- Improve Efficiency & Yield
- Method Performance monitoring

R&D Process Development/ Optimization
- Rapid Experimentation and feedback
- Structured Tech Transfer
- Structured historical knowledge repository

Quality
- Faster Batch release
- Faster/accurate investigations
- Global Batch Traceability

Conclusions

Objectives of PAI Inspection:	ACTIONS
Determine Readiness for Commercial Manufacturing	Comprehensive Process Performance Qualification **Continue design space verification** (characterization data from full and pilot scale, OOT, OOS, Quality Events addressed) GMP Quality Systems Check
Conformance to Application	Batch Record Alignment: Manufacturing records and test methods align with filing Specifications Management: Product and materials conform to filed specifications Change Control: Changes are approved before lot release
Data Integrity Audit	Raw data available and integral

1. *Build efficiency into your initially filed process. Post-approval changes are cumbersome especially if product is marketed in multiple countries*
2. *Ensure data is readily accessible with proper source attribution*

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Why Knowledge Graph?

1

Future Proof

The Data fabric can adapt to new requirements and answer unanticipated questions. It reflects what you did yesterday, and what you are doing today.

2

Brings Meaning to Data

The Data fabric understand the relationships between entities and how those relationships change with time. It highlights the hidden relationships in data- making insight generation easy, fast and robust.

3

Change Resistant

Buying new business, switching ERPs – data fabric does not need to change. It auto adapts to these changes.

4

Extendable and Cross Functional

Data Fabric works across data silos and external sources, regardless of data structures. Extend the Supply Chain data fabric to R&D, Commercial or additional sources for enhanced cross functional insights.

5

Time Congruent

As business changes, rules and relationships change. Data Fabric structure is impervious to these changes. Your insights continue to remain relevant without needing a full redesign.

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