“BACK PACK” MEDICINE, A REAL POSSIBILITY?

NEXT GENERATION BIOThERAPEUTIC ADVANCEMENTS

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PRECISION MEDICINE IS TODAY’S REALITY

Personalized medicine: Time for one-person trials
Nicholas J. Schork
29 April 2013

Precision medicine requires a different type of clinical trial that focuses on individuals, not average, responses to therapy, says Nicholas J. Schork.

Rewriting Life
Backpacks for Cells
Polymer patches hitched to the surfaces of immune cells can transport a variety of cargo.
by Jocelyn Rice November 12, 2003

Understanding Precision Medicine
In precision medicine, patients with tumors that share the same genetic change receive the drug that targets that change, no matter the type of cancer.

Personalized Medicine
Part 1: Evolution and Development into Theranostics
E. Randy Wotring, PhD, RPh, Carol I. Asakura-Izilrah, PhD, and Michael Purcell, RPh, MBA

Personalized medicine, precision medicine, or theranostics is a medical model that separates people into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease.

Wikipedia
CELL THERAPIES LANDSCAPE DEMONSTRATES THIS REALITY

Figure courtesy of PreScouter Inc.
AMGEN’S “BIOLOGY FIRST” APPROACH TO DISEASE REQUIRES WE CONTINUE TO ADAPT OUR CAPABILITIES
PRECISION MEDICINE CHANGES THE MANUFACTURING PARADIGM

Conventional

Key Enabling Technologies
- High titer processes
- Single-use systems
- Modular design and construction
- Connected processing
- Online / At-line analytics
- Real-time remote monitoring
- Raw material variation control

PATIENT BASED, MODULAR AND DISTRIBUTED MANUFACTURING REPRESENTS OUR NEXT PARADIGM SHIFT
INTEGRATION OF NEXT GENERATION MANUFACTURING WITH REAL TIME ATTRIBUTE TESTING

Current Paradigm

Drug Substance Process

Attribute Testing

Drug Product Process

Future Paradigm

Cryo-Vial

Integrated DS & DP Bioprocessing

Device

Health Authority acceptance is integral to this aspiration
TOWARDS THIS, WE ARE ADVANCING THE NEXT GENERATION OF MANUFACTURING FACILITIES, PROCESSES AND INTEGRATED TESTING

- Continuous manufacturing enables facility footprint reduction and increased efficiency

- Modular facilities construction provides on-demand scaling of biopharmaceutical production and laboratory space

- Testing that provides specificity to measure attributes and increases efficiency of testing and product release
NEXT GENERATION MANUFACTURING IS HERE

FROM CONVENTIONAL TO CONTINUOUS MANUFACTURING (CM)
BIOLOGIC MEDICINES ARE MORE HIGHLY ENGINEERED AND DIVERSE

- Product quality drivers
- Supply requirements
- Financial considerations
- Regional manufacturing
- One size does not fit all

APPROPRIATE MANUFACTURING TECHNOLOGIES CAN BE MATCHED TO MODALITIES TO DELIVER TO THE QUALITY TARGET PRODUCT PROFILE (QTPP)

https://www.amgenscience.com/the-shape-of-drugs-to-come/
ADVANCING DRUG SUBSTANCE BIOMANUFACTURING TECHNOLOGIES

Bioreactor scale reduction

1. Industry-first next-gen biomanufacturing facility with regulatory approval
2. Smaller facility footprint and shorter facility build time
3. Ballroom design and increased deployment of single-use components

Footprint reduction using continuous cell culture production

1. Implementation of continuous cell culture process
2. Further reduction of facility footprint
3. Process enables use of all single-use components

Biomanufacturing Dematerialization and Integrated Analytics

1. Integration of at-line and on-line analytics into continuous DS process
2. Further footprint reduction with integrated analytics

1. Integration of at-line and on-line analytics into continuous DS process
Right-sizing biomanufacturing to support Amgen’s polymodal pipeline
2. Further footprint reduction with integrated analytics
THERAPEUTIC DIVERSITY REQUIRES A FLEXIBLE MANUFACTURING NETWORK: TRANSITION FROM TRADITIONAL TO NEXT GENERATION MANUFACTURING

MULTIPLE MANUFACTURING TECHNOLOGY OPTIONS AND MODULAR PLATFORMS CREATE OPPORTUNITIES THROUGH SPEED, FLEXIBILITY AND COST
AMGEN’S NEXT GENERATION AND FIRST IN ASIA MANUFACTURING: AMGEN SINGAPORE (ASM)
DESIGN AND TECHNOLOGIES SIGNIFICANTLY REDUCE ENVIRONMENTAL IMPACT

- Less water for heating, cooling, and cleaning of equipment
- Smaller facility and lower air quality classifications
NEXT GENERATION BIOMANUFACTURING ACCELERATES COMMERCIALIZATION TIMELINE

Traditional

**pilot plant** → **clinical plant** → **commercial plant**

FIH → TOX → Clinical (Phase 1/2) → Commercial Process Development (CPD) → Clinical (Phase 3) → Commercial

Next-Gen Mfg

**pilot plant** → **clinical plant** → **commercial plant**

FIH → TOX → Technology Transfer → Commercial (Phase 1-3) & Commercial

20KL

>5 Bioreactors

4-6 Bioreactors
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FROM NEXT-GEN TO CONTINUOUS MANUFACTURING (CM)

Conventional Facility
750k sq ft

QC Lab | Utilities
---|---
Mechanical Support | Warehouse
Manufacturing | Admin and Amenities

3-4 years for construction

Next-Gen. Facility (e.g. ASM)
120k sq ft

~ 80% Size Reduction With the Same Throughput

18 months for construction

Continuous Manufacturing

3-6 months for construction

Addition within an existing facility can support multiple products

ENABLES FURTHER FOOTPRINT REDUCTION, ACCELERATED FACILITY READINESS, AND FASTER PATIENT ACCESS
DRUG SUBSTANCE LOT DEFINITION:
LOT IS DEFINED BY TIME INTERVAL IN STEADY-STATE PRODUCTION
A HYBRID MANUFACTURING NETWORK OF CONVENTIONAL AND NEXT-GENERATION PLANTS CAN BEST SERVE PATIENT NEEDS

1. Optimized network
   - Continuous Improvement
   - Pursue Operational Excellence

2. Add/convert to flexible plants (MoF)
   - Source/develop new technology
   - Transfer current products to new platform when economically viable
   - Rationalize legacy footprint

3. Expand flexible capacity
   - Build flexible operations based on business needs

Past Dedicated Operations
- MAAb/r-protein focused
- Designed for specific products and SKUs

Factory illustration adapted from Clker.com
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AMGEN’S ASPIRATION IS TO ADVANCE NOVEL TECHNOLOGIES FOR ATTRIBUTE MONITORING AND CONTROL

Sensor technologies
- Proteins and raw material ID

Multi-attribute Method
- Measures multiple attributes
- DS/DP release/stability method
- Replaces 3-6 methods
- Molecule characterization

Automated Liquid Handlers
- TECAN
  - ELISAs (DNA, HCP, ProA ELISA)
  - Auto Sample Dilutions
- ECHO
  - Acoustic droplet ejection technology for improved assay precision and throughput

NMR
- Solid state NMR: Monitor potential for conversion to amorphous phase in tablets
- 1D Profile NMR / 2D NMR technologies for comparability & biosimilarity

Chemical Process Interrogation Platforms
- In-situ probes:
  - particle size measurement - PVM/FBRM
  - on-line reaction monitoring - ReactIR

Process Analytical Technologies
- Flow-based chemistry through novel physical design and software coding.
- Connectivity between sample source and online real-time analytics.

Micro sequential injection (µSI) system
NUMEROUS TEST METHODS ARE TYPICALLY REQUIRED FOR DEVELOPMENT, PRODUCTION AND ANALYTICAL ASSESSMENT

• Total of 30+ assays (13 redundant over DS & DP)
• End point manual testing
• Complex and resource insensitive
• Instrument centric, non PQA specific
ON-THE-FLOOR PROCESS ANALYTICAL TESTING (PAT) STRATEGY: TIES ANALYTICAL ASSESSMENTS TO MANUFACTURING CAPABILITY

- End point manual testing
- Complex and resource insensitive

On-the-Floor Testing Advantages

- Reduce off-line laboratory testing footprint by moving assays on-the-floor and increase logistical resource savings
- Enhance real-time process performance and product quality knowledge to assist quick decision making and in-time material disposition
- Achieved ~80% reduction in assay result turnaround time
- Quality Unit oversight is maintained

IPC: In-process Control
PQA: Product Quality Attributes
MAM ONLINE: REAL TIME PQA MONITORING

• Evaluate product attributes in real time
• Correlate process parameters with product quality attributes

Real Time Online PQA Monitoring

- Oxidation
- Hydroxylation
- Deamidation
- Isomerization
- Clip II
- Clip I
- High Mannose

% of modification

To Establish Connectivity of Bioreactor and Analytical Instrument for Online MAM, Introduced Proprietary Micro Sequential Injection (µSI) Technology

- The Micro Sequential Injection (µSI) technology is essentially a micro-fluidic handling technique with programmable flow to execute sample preparation protocols
- Key components to enable µSI methodology:
  - Syringe pump
  - Holding coil
  - Solvent selector valve
- Functional peripherals can be added to expand the instrument platform

Connectivity of Sample Sources and Analytical Instruments is Established by the µSI Technology
SUCCESSFUL DEMONSTRATION OF ONLINE REAL-TIME MAM FOR 40-DAY DS CONTINUOUS MANUFACTURING PROCESS

μSI-MAM Sample Preparation Process Flow

<table>
<thead>
<tr>
<th>Step</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Acquisition</td>
<td>0.0 hr</td>
</tr>
<tr>
<td>Denaturation</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>Reduction</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>Alkylation</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>Enzymatic Digestion</td>
<td>0.5 hr</td>
</tr>
<tr>
<td>Buffer Exchange</td>
<td>1.5 hr</td>
</tr>
<tr>
<td>LC/MS Injection</td>
<td>2.0 hr</td>
</tr>
</tbody>
</table>

Online real-time μSI-MAM assay system for drug substance Continuous Manufacturing
Online MAM Complemented by Online Titer, Aggregation, Charge Variant, HILIC Glycosylation Assays For Enhanced Process Knowledge

![Titer, Charge Variants, Aggregation, High Mannose (M5) Graphs]

- **Titer**
- **Charge Variants**
- **Aggregation**
- **High Mannose (M5)**

- **3-in-1 µSI-UPLC System** (Titer, SEC and CEX)
  - Bioreactor
  - ProA Capture
  - µSI-HILIC Sample Prep System
  - UPLC for HILIC Assay

Online real-time analytics
Developing and implementing on/in/at-line PAT analytics to modernize Amgen’s biomanufacturing technology capable of:

- Real-time in-process monitoring and control
- Real-time release testing

Enhancing process knowledge for a more robust manufacturing process with fewer production interruptions and product failures, greater assurance of consistent manufacturing with improved product quality and expected clinical performance and availability throughout a product’s lifecycle.
ALSO FOCUSED ON DRUG PRODUCT PROCESS INNOVATION: 
VANRX: A FULLY GLOVELESS ROBOTIC FILLING CELL

<table>
<thead>
<tr>
<th>Container closure configurations</th>
<th>Bulk vials</th>
<th>RTU trayed vials</th>
<th>RTU nested vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready-to-sterilize bulk</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>RTU in ported bags</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>RTU nested plastic caps</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>

Vanrx requires containers and closures in ready to use (RTU) nested format

**Capabilities**
- 1mL nested glass syringe
- Nested glass vial with plastic push-on caps

**Design features**
- **Totally gloveless**: designs out failure modes associated with manual handling
- No conveyance of containers; only pick and place movement by robot
- Horizontal airflow; EM using RCS unit, no settling plates
- Filling isolator can be integrated to Lyo through a lyo integrator

**ChangeOver**
- Tooling Change: PFS ↔ Vials: 40 mins
- Decon Cycle (0.03 ppm): ~4 hours
- Cleaning/Rinsing (as needed): up to 8 hours
- Total: up to 15 hours

**Single Use Systems**
- No closed door assembly
- All RTU single use product path

Vanrx robotic filling systems offers a very unique design for a high mix low volume application
A LOOK INTO THE POTENTIAL FUTURE OF MEDICINE

We live in a moment of history where change is so sped up that we begin to see the present only when it is already disappearing.

- R. D. Laing

- Imagine a time when....
  - Diseases could be diagnosed, and medicines manufactured, tested and distributed, all at the point of patient use
  - Extremely personalized medicine to combat a patient’s specific disease attributes
  - A medicine made at a dose customized for optimal effect and minimal waste
  - Instead of in a hospital, the patient could even be ambulatory
  - Today, a layperson might scoff at this idea, thinking that it is a description of a best-selling fictional novel

- Less than 20 years ago, we pondered the problem of completely sequencing the human genome
  - Today, we are exploiting that genome to identify optimal disease targets and create the “futuristic” medicines of today

https://images.unsplash.com/photo-1530620027689-2bd5b849d329?ixlib=rb-0.3.5&ixid=eyJhcHBfaWQiOjEyMDd9&s=4f982d8080ad6cc8bd9ecbe66e5737c17&auto=format&fit=crop&w=1350&q=80
BUILDING AGENCY AND INDUSTRY ACCEPTANCE OF NEXT GENERATION ADVANCEMENTS REQUIRES BALANCED ENGAGEMENT

Industry Intentions

Next Gen Advancements
Regulations, guidances, tools, philosophies, industry best practices

Regulator Acceptance

New Paradigms
Quality, Manufacturing, Modalities, Prior Knowledge, etc.

Range of Potential Perceptions

Education of and by sponsors

Some reactions: “too slow”

Some reactions: “too risky”

Education of and by regulators

Agency Thinking

New Approach

Timely Review Acceptance and Implementation

Ability to Effectively Inform, Communicate and Implement
### SUMMARY

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<tbody>
<tr>
<td>1</td>
<td>External and internal factors are driving changes in biotechnology production which require new operational capabilities and flexible manufacturing operations</td>
</tr>
<tr>
<td>2</td>
<td>Advancements in attribute based testing paradigms can now be leveraged</td>
</tr>
<tr>
<td>3</td>
<td>As an industry we need to continue to advance progressive Next Generation Advancements to further optimize innovative drug development to deliver personalized medicines for patients around the world</td>
</tr>
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THANK YOU
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QUESTIONS?