Manufacturing Technology and Supply Chain Trends

Maurice Parlane
New Wayz Consulting Ltd
CBE Pty Ltd

Overview

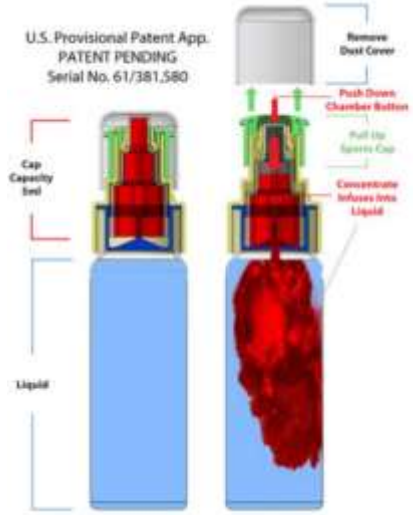
Technology advancements

- Innovative presentations
- Single use technologies
- Pre-fabricated facilities
- Process analytical technology and continuous manufacturing

Supply chain advancements

- Process robustness
- Supply chain resilience

Pack Innovation/Differentiation



NATURAL HEALTH PRODUCTS NZ®

Pack Innovation/Differentiation

Considerations

- Easier adoption for lower risk or consumer products
- Capital and set-up costs can be challenging
- Local support may be a factor
- Potential product cost differentiator; however, can be a double-edged sword for supply or manufacture where reliant on CMOs
- Longer supply chain and less options if delays occur
- GMP products can be more challenging due to need for shelf life/stability evidence

Single Use Technologies

Implementation Drivers

- Potential "game-changer" for GMP
- Flexible – saves time and can cope with development changes and scale up.
- Many applications. Not just liquids mixing, holding, transfer, fill and finish.
- Extremely rapid growth in available technologies
- Can present enhanced levels of containment or process closure
- Often requires considerably less space for process
- Can present significant project delivery cost and timeline benefits

Single Use Technologies

However…

- Careful technology evaluation is required
- Procurement and storage requirements are a factor
- Product cost can increase
- Increased reliance on vendor network
- Operations and support staff need to be carefully trained in correct use
- SUT is demanding for the business to manage (purchasing, validation, QA)
- Pack change control can be an issue

Single Use Technologies

Technical aspects

- Not Reactive, additive or absorptive to the product

Test Considerations

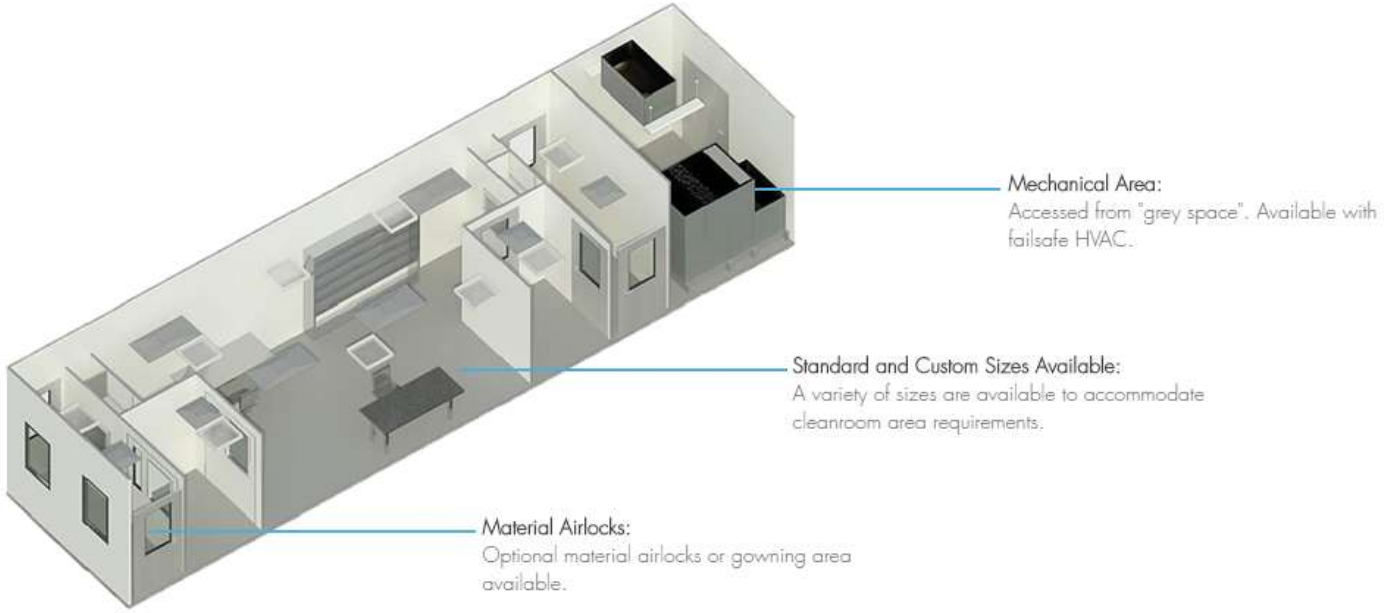
- Material compatibility (chemical resistance)
- Leachables or Extractables
- Biocompatibility
- Animal origins
- Particulate control
- Bioburden/Bacterial Endotoxin
- Absorption
- Re-use consequences

Regulation (EC) No 1935/2004

21 CFR 174 – 178

Pre-Fabricated Facilities

1. Containerisation
2. Pre-Fabricated or proprietary (clean rooms/laboratories)
3. Turnkey (e.g POD™) pre-fabricated facility (may include equipment) - Build and FAT off site then shipped to site with SAT documents



Pre-Fabricated Facilities

Recent examples of use of pre-fabricated facilities

- Pfizer/GSK "PCMM" collaboration (Portable, continuous, miniature. manufacture) facilities. Includes tabletting unit process equipment. [ISPE FOYA award]
- Covid-19 testing pop-up labs and vaccination hubs (Australia)
- Pharmaceutical compounding cleanrooms (AU/NZ)
- Medicinal cannabis pilot plant facility (NZ)
- Small scale aseptic formulation and filling (University in AU)
- Dairy factory (IF) laboratory expansion (South Island, NZ)

Pre-Fabricated Facilities

Pros…

- Short timeline
- Turnkey approach and reduced concept design times
- Fully commissioned
- Transportable

Cons…

- NZ Building Act/Fire Regulations compliance (BRANZ)
- Access – off the ground for lower cost
- Up-front CAPEX cost
- Planning for installation must be right – omissions

Process Analytical Technology (PAT)

Current efforts are largely analytical e.g.

- Raman or NIR spectroscopy for ingredient ID
- End point NIR based spectroscopy for drying, blending, assay/content uniformity, water content, polymorphic forms, process quality attributes.
- In-line PSD measurement for particle size at milling/spray drying
- FBRM (Focused Beam Reflectance Measurement) – real time measurement of dimension and number of crystals

Tendency to batch process means analytics are commonly used **at-line** for in-process control of unit processing, particularly in powders; however often not in-line with feedback control.

Process Analytical Technology

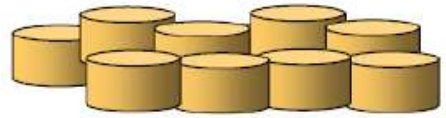
Emerging trends.

- Real time laser diffraction particle size for spray drying or milling/classifying
- NIR at-line for blend, granulation and compression parameters
- Move away from traditional unit processes to those which are more suited to PAT, e.g. spray drying and roller compaction
- Benchmark other sector applications
- Incorporation of feedback control

Tablet manufacture example

Chemical/physical RM properties
Particle size distribution (granulation)
Concentration and uniformity (blending)
Weight, hardness and assay (compression)
Imaging (coating)

Process variables in Dissolution model (release)



Real-time Release

Continuous manufacturing example

Challenges:
Ingredient ratio control (~2 sec)

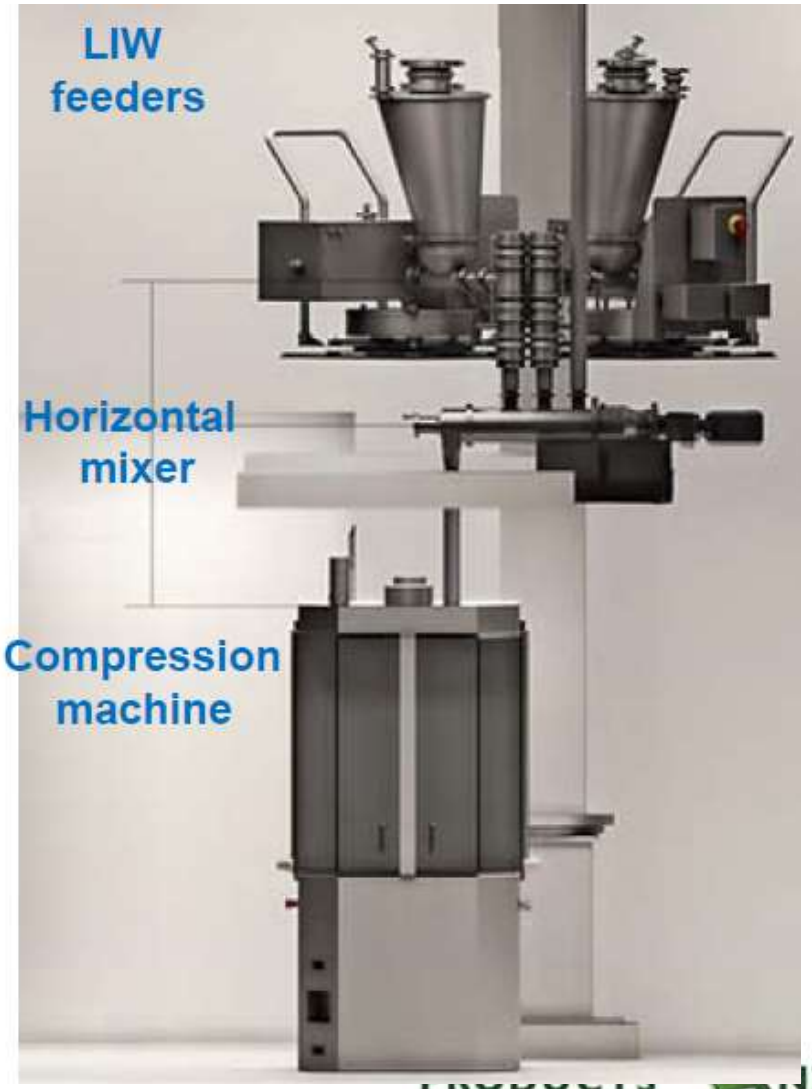
At line concentration measurement and blend control (~1.2 sec)

Compression control, measurement and reject actions

Continuous dispensing/feeding

Continuous blending

Continuous tablet compression



Jonathan Wade, PhD., "Continuous Validation Lifecycle for a Direct Continuous Direct Compression Manufacturing Process"
ISPE Process Validation Conference, Oct 2019

SCIENCE underpins the use of technology…

Observations on status of manufacturing science and quality

…. "What are we learning"

All is not well (Quality vs Compliance)

Problem acceptance.

- Some products are not well designed and/or lack robustness
- Increased awareness that process knowledge/understanding is lacking or inadequately transferred – leading to issues with product quality
- Outsourcing or long supply chains can lead to delays which ultimately can impact customers (increased occurrence of shortages)
- These issues are inter-related…

Despite having a highly regulated GMP environment, Quality appears to be either deficient or a major factor in current GMP concerns…..

Quality vs Compliance

Industry responses.

- Increased focus on supply chain robustness (and potentially duplication of supply)
- Increased focus on process robustness
  - Quality by Design (new and existing products)
  - Process/performance verification (trending)

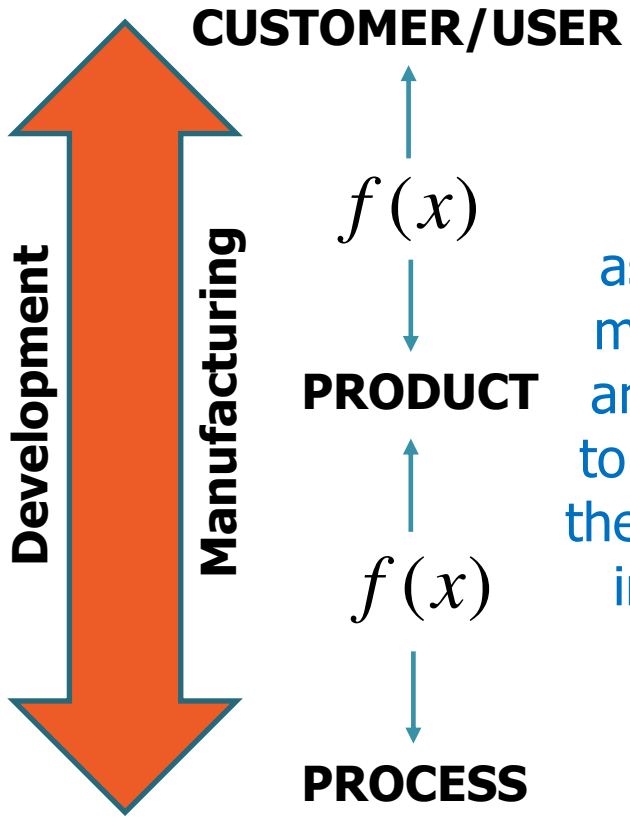
Robust process = A process able to meet quality standards or specification under the influence of variations from its inputs

Quality by Design (QbD)

Understand & define customer requirements (Quality Target Product Profile) [statement in terms of the user]

Undertake product development to design a suitable product (Critical Quality Attributes)

Design the process and controls to meet product attributes (Critical Process Parameters and Material Attributes)



Use risk assessment, mathematics and statistics to understand these functions in scientific terms

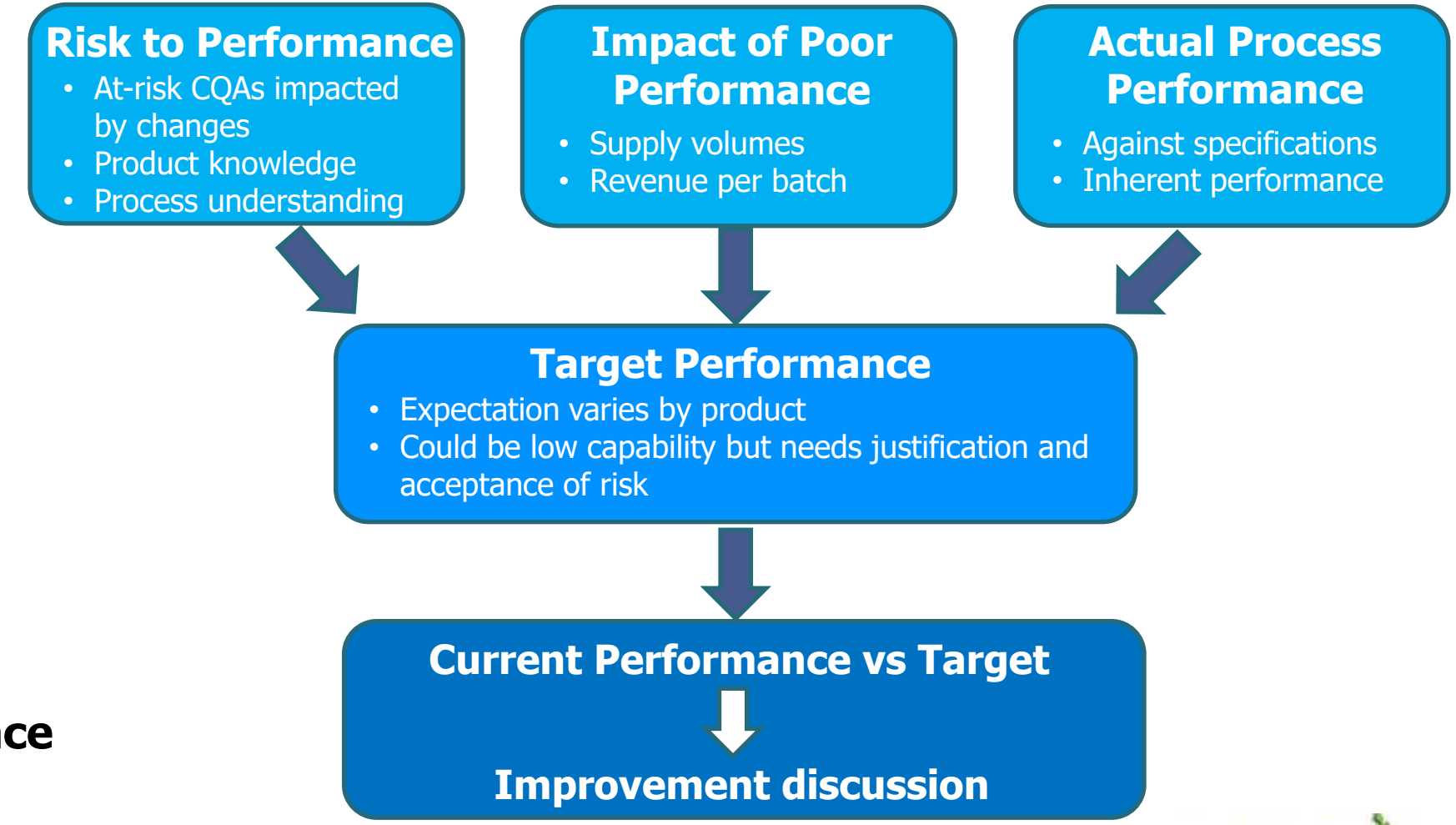
A fundamentally different way of considering risk

Process Robustness

Assess Risks

Develop Targets

Assess Performance

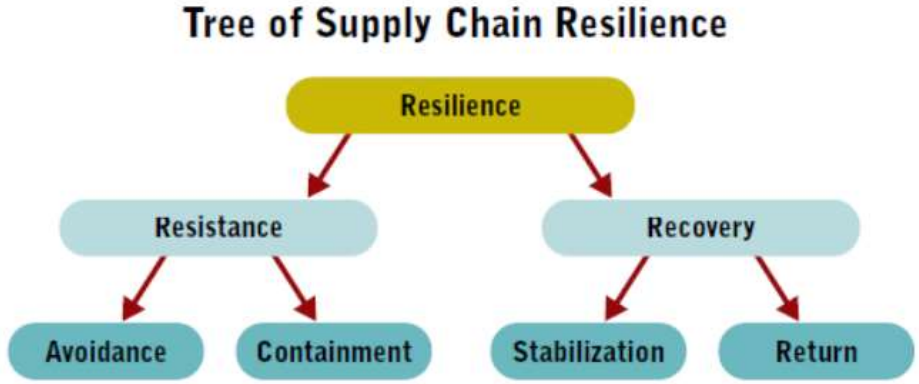


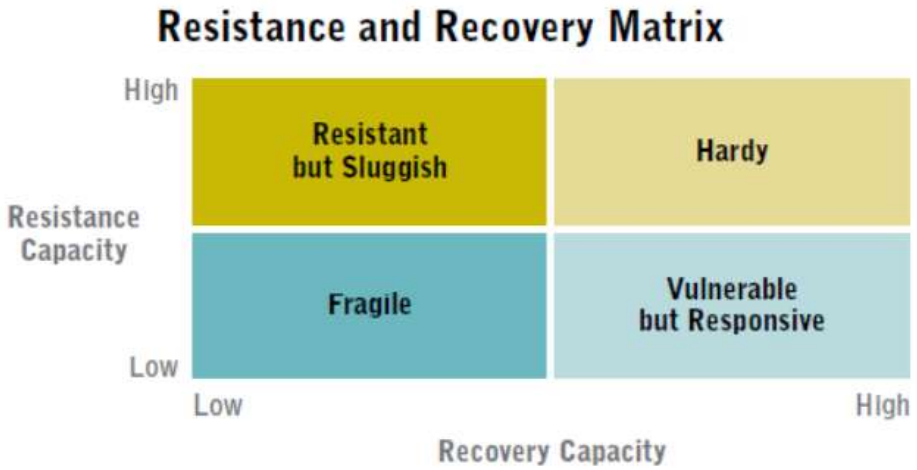
Supply Chain Resilience

Two dimensions.

- Understand capacity to **resist** potential issues by avoidance or containment
- Plan measures to **recover** by stabilisation or speed to return to normal situation

Both resistance and recovery frequently result in consideration of risk associated with single sources of supply





Supply Chain Resilience

Achieving duplication of supply can be difficult to achieve in a cost or commercially effective manner

- Impact to product cost and supplier responsiveness for "shared" supply arrangements
- Ability/cost to hold capacity "available" at supplier
- Management of relationship with previously key supplier

Practical options

- Group purchasing arrangements
- Acceptance of larger safety stocks (lean vs robust)
- Take or pay contract arrangements
- Insourcing or integration of high risk supplies
- Pragmatic assessment of the need for resilience vs cost to achieve this across the business (e.g. 80/20 rule)

Summary

- Innovation, cross industry benchmarking and new product demands are driving technological advances in a number of new areas
- There is an increasing reliance on specialist vendors and proprietary technologies in this area.
- Process understanding is a significant underpinning capability to application of advancing technology
- The life sciences industry has historically been a slow adopter of new technology – often citing compliance as justification for not needing this
- Compliance does not necessarily lead to high levels of quality, despite this perception; however regulatory compliance is necessary.
- Industry and regulators are focussing more on the need for **quality** to be designed into products (Quality by Design) and on the role that process and supply chain robustness plays in this objective.

Thank you

Maurice Parlane, CPEngNZ
Principal/Director,
New Wayz Consulting Ltd,
Auckland, NZ
www.newwayz.co.nz

Director
CBE Pty Ltd
VIC, Australia
www.cbe-ap.com.au

Mobile: +64 21 650 692
maurice.p@newwayz.co.nz