

# Business Case Insights for Continuous Manufacturing

CMAC and PwC

IN ASSOCIATION WITH



**CMAC**  
FUTURE MANUFACTURING  
RESEARCH HUB

# Setting the Scene

This document seeks to review key considerations for building a successful business case for the industrial adoption of innovative Continuous Manufacturing (CM) technologies. The report is written from the perspective of the CMAC manufacturing research programme stakeholders. Hence it targets factors directly relevant to continuous small molecule pharmaceutical manufacture and although addresses the many drivers and impacts across the entire value chain, brings a strong emphasis on factors relevant to continuous Drug Substance (DS) manufacture.

Clearly the ultimate benefits in cost, speed, performance and quality from CM must be realised within manufacturing organisations, however the impact on development approaches and timelines in R&D must also be considered. There is therefore a need to establish new digital tools, smart development platforms and optimised experimental design approaches to support rapid decision making, efficient deployment of resources and critically, to minimise development timelines. With this focus on advancing CM, the authors recognise that given the substantial efforts to increase our underpinning knowledge and technological capabilities, there will inevitably be benefits that can improve both batch and continuous processes. Whilst continuous Drug Product (DP) manufacturing has already been proven, with several products now on the market, and fully integrated end-to-end continuous processing concepts have also been demonstrated, it is likely, particularly for DS manufacture, that the deployment of hybrid batch-continuous operations will grow in the short term.

It is important too to recognise the need to enable CM adoption both within organisations as well as across the supply chain, for example in Contract Manufacturing Organisations (CMOs). With the associated growth in new technologies and services comes the opportunity for different business models that exploit CM to deliver additional value and tackle major challenges facing the sector: how are we to manage spiralling prescription medicine costs in the NHS and other global healthcare systems; can the pharmaceutical supply chain deliver greater personalisation of medicines quickly and cost effectively; can the security of global medicines supply be assured to maintain access to essential medicines or respond to medical emergencies; how can the impact of medicines manufacture on the environment be minimised and made more sustainable? Those that can best harness the potential of innovative technologies such as CM will be best placed to meet these challenges.

This Business Case Insights for Continuous Manufacturing was undertaken with engagement from CMAC Tier 1 partners AstraZeneca, Eli Lilly, Pfizer and Takeda as well as leveraging CMAC's own extensive academic portfolio on end-to-end (E2E) processing. CMAC would like to thank all those who have contributed information and viewpoints on key technical aspects in combination with PwC's wider business case perspective, to help inform and engage senior stakeholders and drive continuous manufacturing forward.

# Contents

<a href="#">Executive summary</a>	<a href="#">4</a>
<a href="#">Continuous manufacturing through 9 lenses</a>	<a href="#">6</a>
<a href="#">Industry 4.0- The future of pharma</a>	<a href="#">8</a>
<a href="#">Revolutionising the current value chain</a>	<a href="#">10</a>
<a href="#">Improved production, reduced waste, lower cost</a>	<a href="#">12</a>
<a href="#">The risks of implementing new manufacturing processes</a>	<a href="#">14</a>
<a href="#">Learning from the extensive published information</a>	<a href="#">16</a>
<a href="#">Leveraging CM to bring commercial advantages</a>	<a href="#">17</a>
<a href="#">CMO strategy</a>	<a href="#">18</a>
<a href="#">A new dimension to enhancing R&amp;D agility</a>	<a href="#">19</a>
<a href="#">Identifying CM value in the pipeline</a>	<a href="#">20</a>
<a href="#">A regulatory roadmap</a>	<a href="#">21</a>
<a href="#">Enabling and enhancing Quality Management Systems</a>	<a href="#">22</a>
<a href="#">Defining value from continuous versus batch manufacturing</a>	<a href="#">23</a>
<a href="#">The impact of tax</a>	<a href="#">24</a>
<a href="#">Legal opportunity</a>	<a href="#">25</a>
<a href="#">Examples of CM facilities around the world</a>	<a href="#">26</a>
<a href="#">Implementing CM in your business</a>	<a href="#">28</a>
<a href="#">References</a>	<a href="#">30</a>

# Executive summary

Continuous manufacturing has a significant role in the future of pharmaceutical manufacturing. It offers unique opportunities to reduce the risk and cost associated with scale-up/transfer from development to commercial sites. Along with the ability to flex the supply chain, according to demand, it offers competitive advantages not provided by traditional batch manufacturing.

Continuous manufacturing is a technology well established across wider industries. From petrochemicals to automotive manufacture, quality improvements, supply chain flexibility and higher overall equipment effectiveness (OEE) enable increased margins and provide a platform for the latest technologies. In this future vision, we aim to define the business case for continuous manufacturing as a direct replacement for current batch manufacturing processes taking place, whilst demonstrating what is possible in an industry defined by its manufacturing process limits.

The benefits of continuous manufacturing when compared to the current batch processes are both immediate, as evidenced in this document, as well as more adaptable to long term industry trends. With rapidly changing healthcare models, the requirements of pharmaceutical manufacturing processes are going to change significantly in the next 10 years. Faster production, more flexible processes and reduced lead times are going to become the requests from across your business as the current PharmaCo operating model is forced to adapt to this new environment.

60-70% footprint reduction

1

## Significant technical improvements

5-15% API yield increase  
1, 2, 6

Waste reduction between 33 and 87%  
5, 9, 21

More consistent product  
3, 7, 8

Reduced factory footprints by >25%  
4, 10, 11, 12, 21

Advantages in every aspect of manufacturing, leading to enhanced processes at a reduced net cost

## Opportunities for innovation across the business

Reduced product lag time

Location flexibility

Real-time quality data

Faster process development

Improved flexibility in production enables significant change across the business to bring the pharma industry in line with other industries

## Potential for true commercial advantage

New CMO strategy

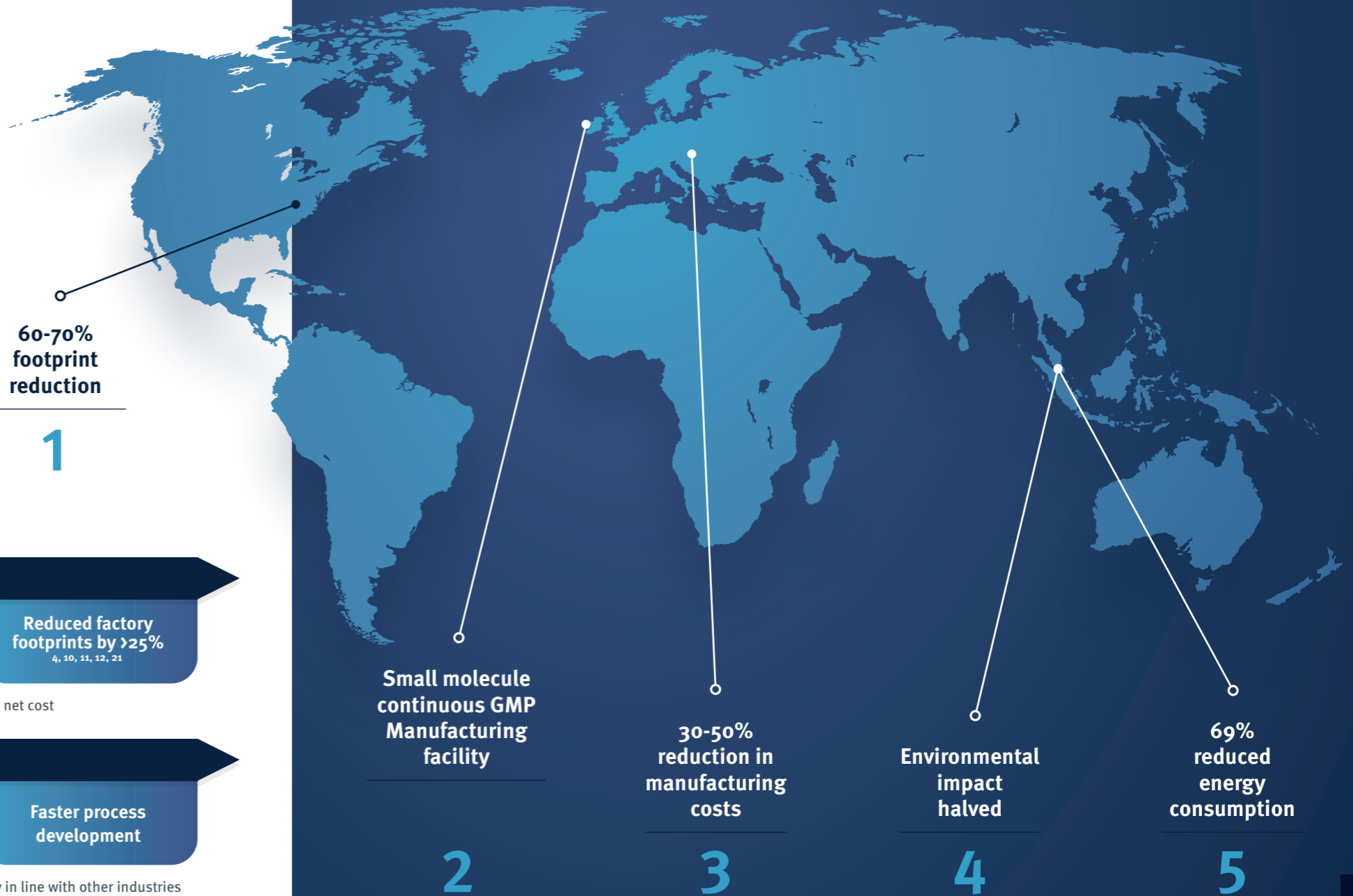
Faster to market

Tax optimisation

Demand matching capability

The opportunities provided can enable a PharmaCo to make radical changes to its operating model and capture markets faster to deliver significant financial return

# Examples of CM from around the world

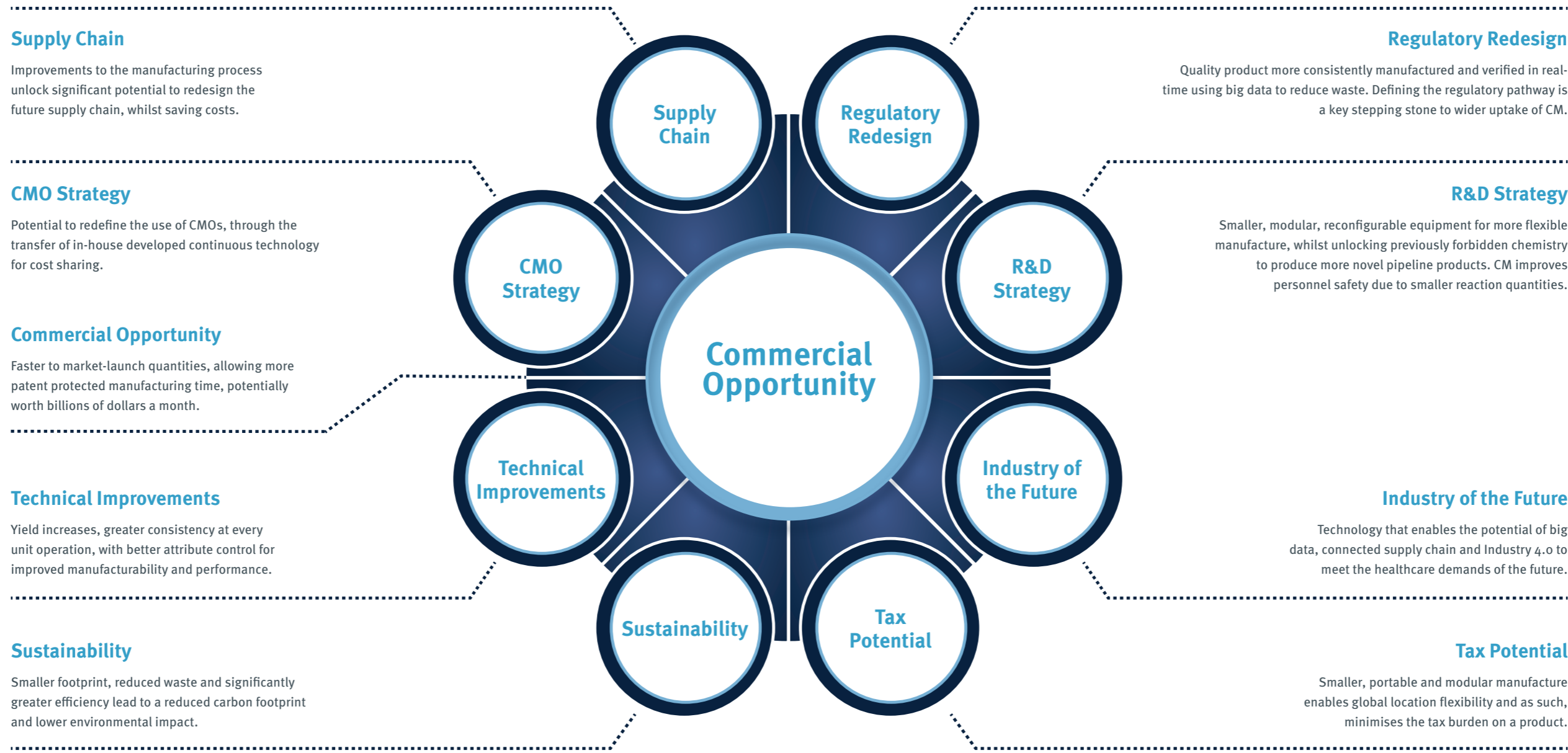


\*ALL REFERENCES CAN BE FOUND AT THE END OF THE DOCUMENT

\*DETAILS ON THESE SITES CAN BE FOUND ON PAGE 26

# Continuous manufacturing through 9 lenses

The opportunities and considerations for implementing continuous manufacturing have been established by assessing their impact through 9 lenses. These lenses enable us to view continuous manufacturing from different perspectives of the business, in order to understand how changing manufacturing processes will impact their business.



## The lenses don't change when considering the product

The related business cases predominately stay the same when looking at different small molecule products or peptides and monoclonal antibodies.

## The lenses also don't change between drug substance and drug product

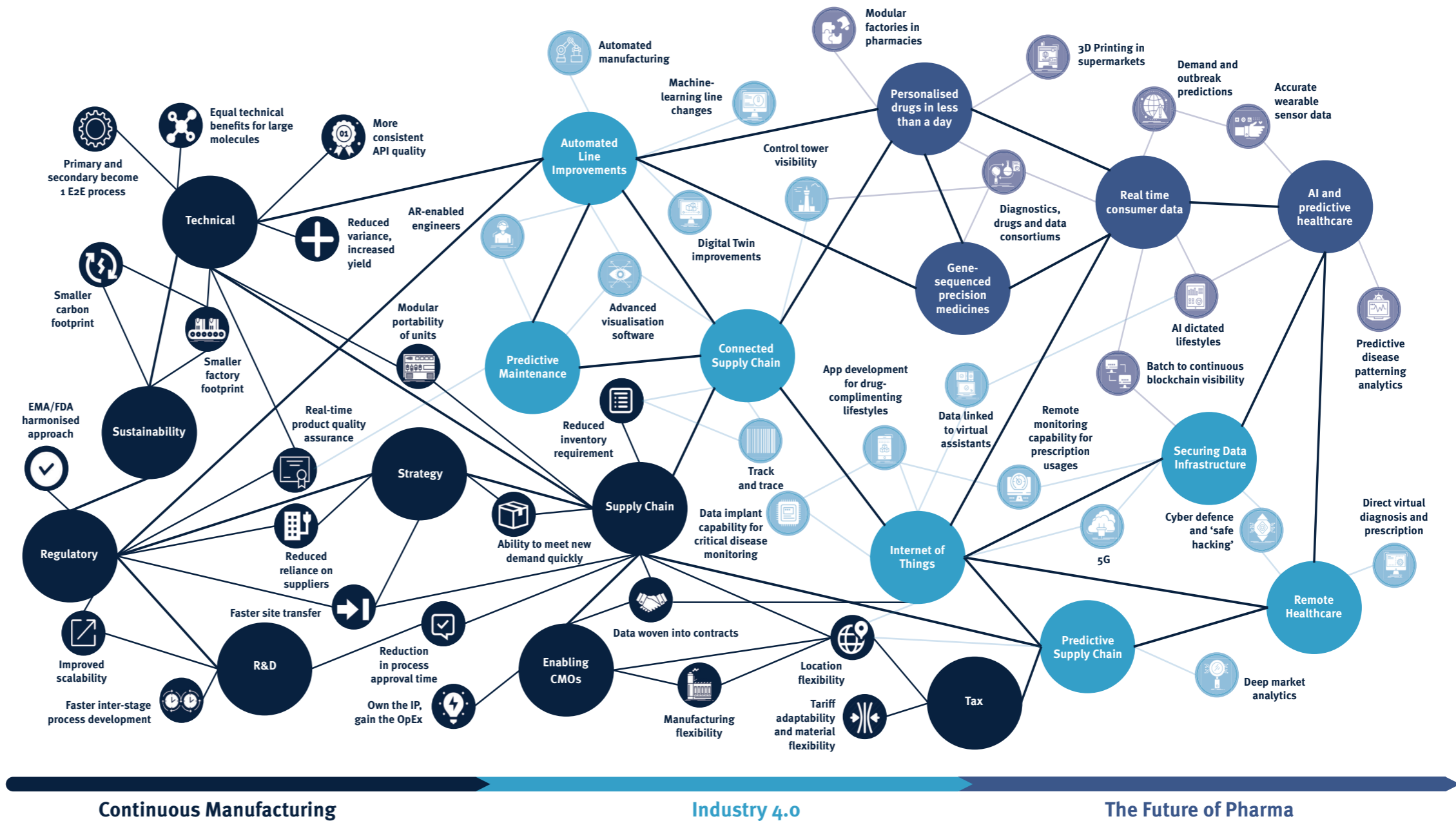
Most of the fundamental benefits are the same regardless of whether CM is implemented in drug substance or DP manufacturing. Differences do exist however, when comparing the technology readiness of equipment and the variety of equipment required. CM in drug product is well established with a range of off-the-shelf equipment available for a relatively small number of unit operations. DS does have a range of equipment commercially available however linking E2E units is limited and the range of conditions in synthesis, work-up or isolation can be broad. Thus, different business cases are often required for DP vs DS although the fundamental benefits are the same. <sup>33</sup> (Additional information via CMAC Tier 1 discussions)

# Industry 4.0 The future of pharma

## Meeting the demands of future healthcare

The next 20 years will see significant change in the healthcare industry as rapid developments in technology drive the use of data to deliver services and products faster, further and more precisely. For the industry to meet the demands that this will set, a significant review and redesign of the entire pharmaceutical company model will be required.

The infographic (right) demonstrates that CM and Industry 4.0 are crucial for the Pharma industry to meet future healthcare demands that include improved efficiency, agile manufacturing and personalisation.



## OPINION LEADERS:

“AI can learn from large data sets to interpret information”

“Data is the foundational infrastructure of process automation, monitoring, process control, in silico design, machine learning.”

“Digital is an enabler of CM. Large datasets need to be structured for ease of storage, fault detection, interpretation, and prediction of process conditions.”

“Real time monitoring is essential for CM as part of Quality by Design (QbD) rather than Quality by Test (QbT). It is essential for CM to enable early detection and prediction of conditions and enabling process control.”

## What is Industry 4.0?

Industry 4.0 is a development from the introduction of digital technology to a fully interconnected environment between machines, devices and people. This approach offers ‘smart factories’ where machines are augmented with wireless connectivity and sensors to create a virtual copy of the entire production line to control and make decentralised, data-driven decisions at short notice. Breakthroughs in robotics, Artificial Intelligence (AI), biotechnology and 5G will all further drive industries to adopt the industry 4.0 approach as best practice.



## How does CM fit in with Industry 4.0

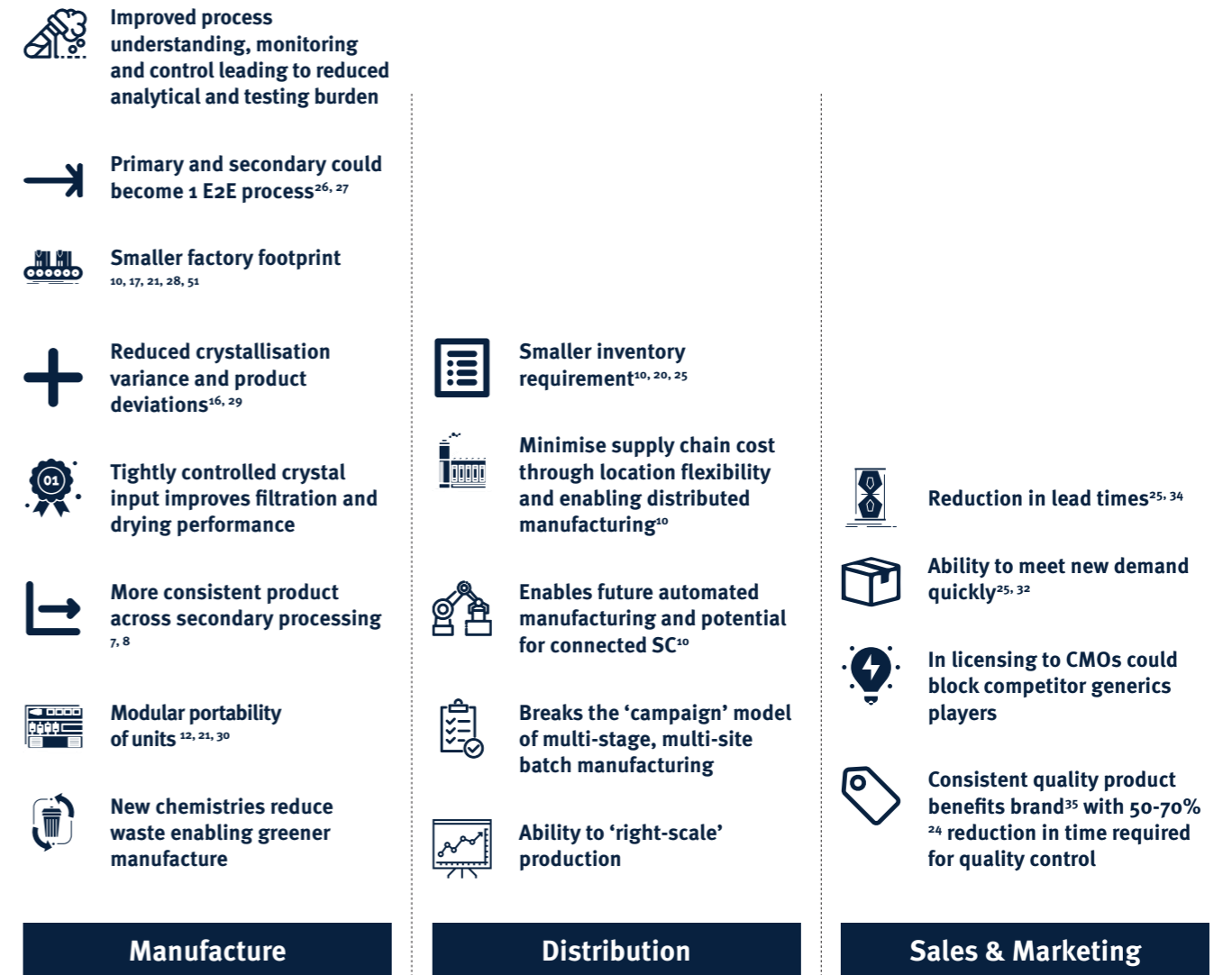
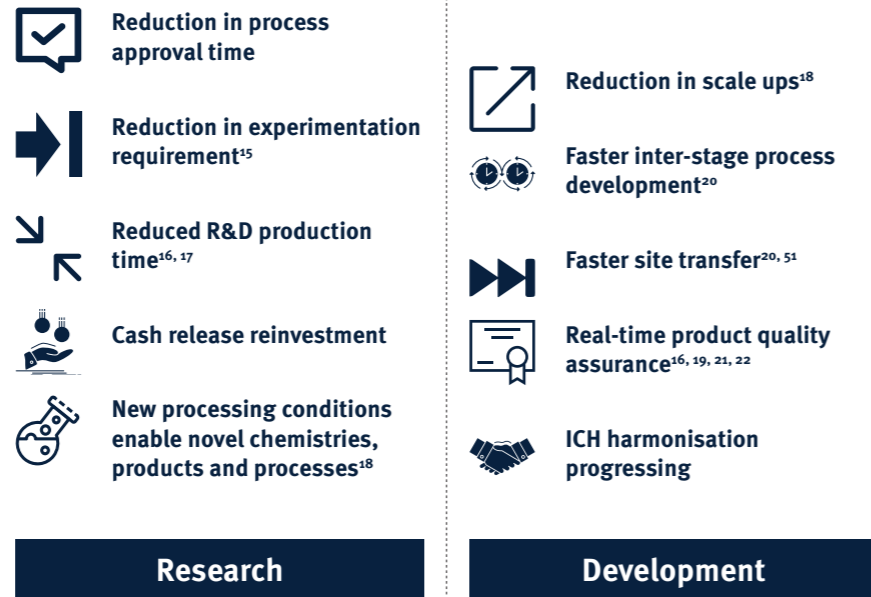
With the benefits of Industry 4.0 being well established, it is important to consider whether CM is compatible with this future vision of the industry. Pfizer’s €50 million CM DP facility in Freiburg, Germany, provides valuable insight as to what Pharma 4.0 could look like.

At the Freiburg DP facility, billions of data points are recorded and analysed every millisecond<sup>14</sup> offering precise quality recordings, reducing the need for lab testing and sampling. This increased quality assurance allows faster medicine approval and release. The CM system significantly increases flexibility to market conditions with outputs being adjusted in minutes, compared to 4 months previously. Material

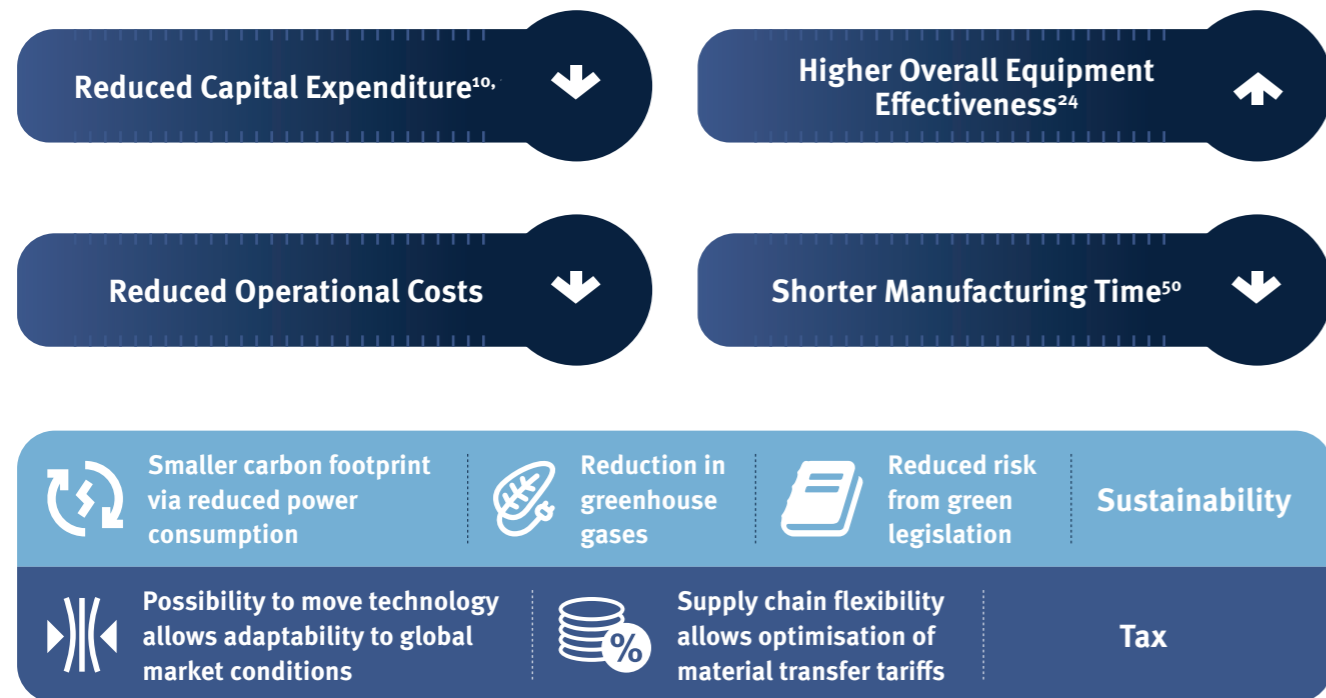
transport and manufacturing parameters are managed through integrated storage spaces as well as automated weighing and electronic process documentation systems.

# Revolutionising the current value chain

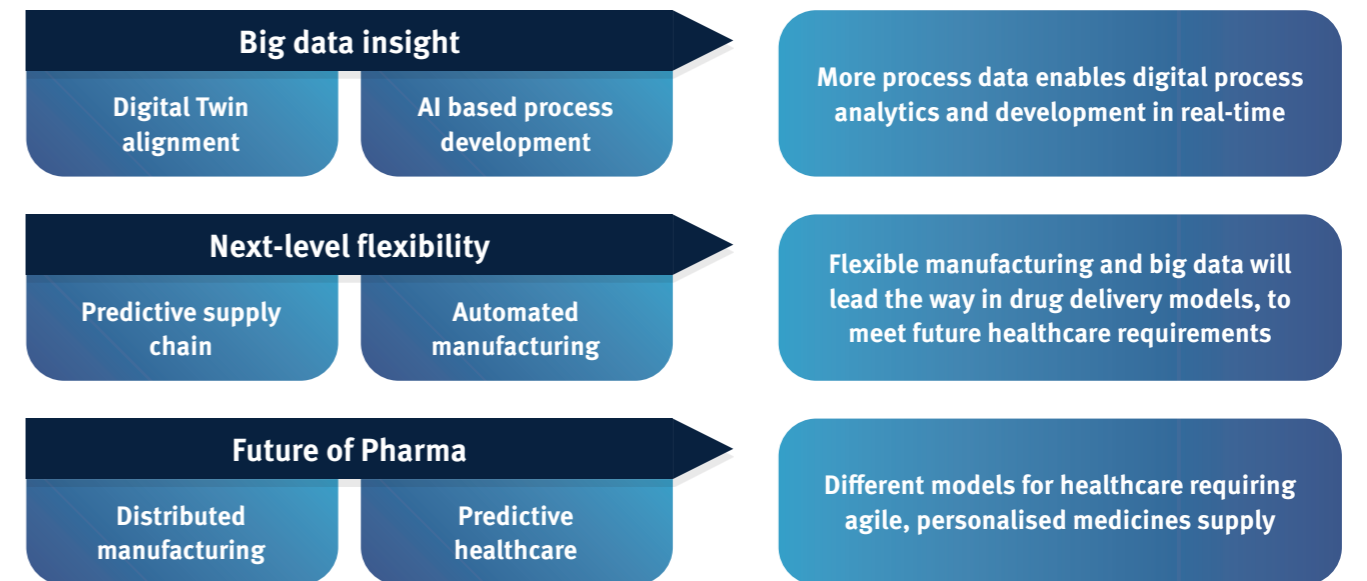
The potential benefits of continuous manufacturing can be mapped across the entire pharmaceutical process. In order to understand the true returns on any investment in this technology, the whole picture needs to be considered.



## WHAT'S POSSIBLE RIGHT NOW WITH CM?



## WHAT DOES CM START TO ENABLE?



The change to continuous manufacturing is therefore a **strategic decision** that makes sense both in the **short and long term**, enabling a business to **meet the demands** that the **future healthcare model** will put to pharmaceutical manufacturing, whilst delivering **significant benefits** across more than just the manufacturing process.

# Improved production, reduced waste, lower cost

The technical benefits of continuous manufacturing are well documented in scientific literature, with the potential to produce both drug substance and drug product at a faster rate, more consistently and with a smaller footprint than traditional batch. In addition to this, the controllability of a continuous system provides opportunities to produce products that are too complex for a batch process to produce successfully.

## API Synthesis

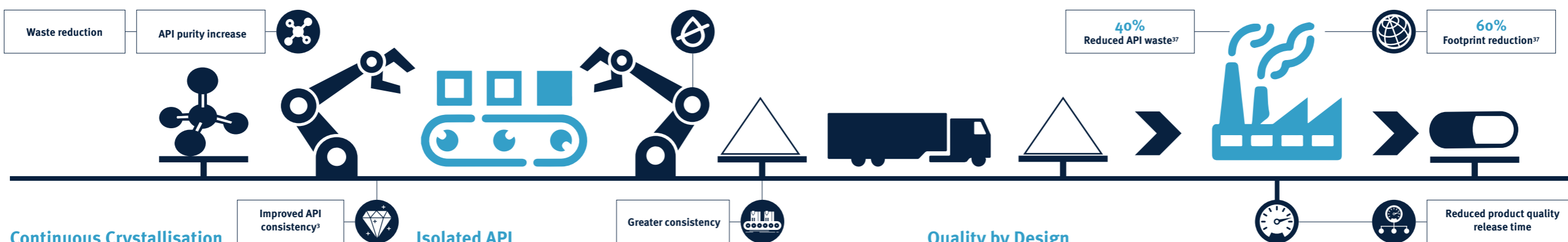
API synthesis through flow chemistry has the potential to produce material with far greater consistency in specification than a batch system, with an improvement in both yield and purity. This has a downstream benefit of providing much more consistent product, potentially producing a reduction in waste, without taking into account changes in the process downstream.

## Filtration and Drying

Moving into the isolation steps for the drug substance, current filtration and drying technologies don't offer significant direct benefits over traditional batch. However there is evidence of a marked performance improvement measured through the feeding of tighter specification material into filtration and drying unit operations<sup>49</sup>.

## Secondary Manufacture

In secondary processing, the combination of API with excipient into the product formulation, and the subsequent processing and tableting arrangements, is an area where significantly more established technologies are starting to be used. Prebuilt and standard units are commercially available, at a wide range of scales, providing a single-unit path from separate API and excipients, to final tablet product. These units have reported increases in energy efficiency of 50%, reductions in product waste and a 60% reduction in required space.<sup>4,37</sup>



## Continuous Crystallisation

Continuous crystallisation provides the opportunity to produce API crystals with much tighter specifications than a traditional batch process<sup>16</sup>. The crystal attributes can also be better controlled, with the ability to adjust the size, shape<sup>38</sup>, and other properties<sup>39</sup> of the crystal to have significant impact in further downstream processes. In addition to this, the nature of a flow chemistry production step allows significantly more control over the reactions taking place, allowing more complex chemistry that can create molecules and crystals previously too challenging to produce in batch unit operation<sup>40</sup>.

## Isolated API

This isolated API from a continuous production can be produced with a variance of only 6σ, compared to a current batch process standard of 3σ<sup>40</sup>. By reducing the variation by 50%, this will reduce the amount of API sent to waste/reworked for being out of specification, providing significant cost benefit to the manufacturing process.

## Quality by Design

During the operation of a continuous process, the use of in-line analytical measurements can indicate the quality of the product leaving the system. This technology has the potential to enable real-time quality testing, reducing or even eliminating the requirement for end-of-line testing of product to statistically establish quality. The use of indicative sensors over the entire process enables real-time feedback control, which can immediately spot variance, and use modelling within the design space to make changes to the upstream process to bring product back within specifications<sup>16, 29</sup>, minimising waste end-product and generating significant savings. Some manufacturers practice transporting product under quarantine, however this is accompanied by potential risk and associated cost, which would be eliminated by real-time release.

## Reduced Factory Costs

The footprint of a continuous manufacturing unit is significantly smaller than batch. This is added to by the significant reduction in the number of human interventions required between unit operations. In a continuous primary manufacturing system, it would be possible to go from drug synthesis to isolated API ready to be moved to secondary processing, without a single human interaction. This has the potential to almost eliminate the number of human error issues occurring during the manufacturing process. There is also potential to run an E2E continuous manufacturing site.

## Modular MicroFactories

The smaller unit operation size provides the opportunity for modular designs, in which MicroFactory scale equipment can be built into standard sized blocks. Universal connectors would allow an approach to factory design with unprecedented flexibility and mobility<sup>41-43</sup>. These units would also enable 'scale-out' rather than 'scale-up', through adding more units rather than increasing unit size, which has the potential to significantly reduce the time and regulatory burden of the current scale-up process.

## Innovative E2E Design

A system in which there is a continuous process right from API synthesis to final drug product provides the opportunity for a variety of innovations that could fundamentally change small molecule manufacturing.<sup>26, 36</sup>

Whilst current regulations require a clearly defined API, it has long been acknowledged in academia, for example, that a system in which excipient could be added to compounds during crystallisation or isolation would enable the creation of more consistent, better controlled products. This could reduce the number of secondary mixing stages, saving on capital expenditure and further reducing the factory footprint. Industry examples of systems such as this are starting to be presented to regulators, and could quickly gain momentum and become the norm.

# The risks of implementing new manufacturing processes

A change in the manufacturing process will have impacts across a pharmaceutical business. Whilst the potential benefits have been discussed, realising these will require well structured change management across all aspects of the business.

## CONSISTENT CHANGE MATRIX

### Planning

- Determine what change will happen
- Plan the roll-out
- Identify the stakeholders
- Understand the challenges

### Communicating

- Senior buy-in, demonstrated to the business
- Constant and consistent communication and updates

### Training

- Identify capabilities within your business
- Train in-house new capabilities where possible
- Hire to fill gaps where required

This process needs to be applied across the entire business, including manufacturing, supply chain, R&D and regulatory

#### R&D

- Skills and knowledge upskilling required to move to CM and new equipment
- Workflows to select “best” technology early during development work not widely adopted whereas batch is “safe” option
- Deeper level of process understanding required for CM, so although can do more reactions, development time not always reduced
- Development of integrated multi-unit continuous operations takes longer than batch equivalent
- More material required for development in drug product

#### Manufacturing

- External supply chain needs upskilling, investment and equipment matching to in-house capabilities
- Plant-wide up-skilling and investment required
- Strategic direction required for CM options
  - CM i.e. Hybrid (part CM, part batch plant) cheaper, easier entry as can retro-fit to existing batch plant, but less overall benefit.
  - Fully continuous different plant design required, but maximises benefit

#### Regulatory

- Update needed to internal regulatory process to allow technology flexibility
- PAT testing requires a scientific approach to quality assurance

Only through understanding these challenges internally can the full value of continuous manufacturing be realised.

#### Supply Chain

- New upstream and downstream supply demands, requiring increased agility in logistics

These risks are compounded by significant changes in culture and ways of working within your organisation.

#### Organisational

- Strategic need to invest generally in capability and not require each unit operation to stand on its own business case
- By the time data is collected to build business cases, often too late or perceived as too risky
- Quantitative business cases shared

## OPINION LEADERS:

“Unlocking the flexible batch size could revolutionise our supply chain”

“The key to implementing continuous manufacturing is to get better at the journey from discovery to commercial manufacture.”

“We have to educate both our internal teams and external partners in order to drive the uptake of CM. This starts with an initial investment, both in our technologies and our people.”

“The investment in new digital infrastructure around the manufacturing process should not be underestimated, and has the potential to impact implementation costs and timelines.”

## APPROACHES TO OVERCOMING CHALLENGES AND REDUCING RISK

Many companies are now working in pre-competitive industry-academia consortia to share the cost of developing and testing technologies and pooling expertise in order to accelerate and leverage their investments.

One such collaboration is CMAC, with 8 large pharma, 7 Universities and 18 SMEs. Working collaboratively to develop new workflows, MicroFactories and Digital Twins to streamline and accelerate development and advanced manufacturing operations. This approach delivers a skilled talent pipeline with industry relevant knowledge and ways of working.

### WITHIN YOUR BUSINESS

#### Collaboration across the business

- A key factor identified for success in the implementation of CM is working as multi-skilled teams from across the areas of the business
- This drives uptake of the new technology, whilst allowing for fast problem solving and broad education

#### Collaboration up the business

- Leadership teams and strategic decision makers should also collaborate across function when reviewing outcomes and making decisions
- Aligning the strategies through the business, with regular progress updates feeding into leadership discussions enables fast decision making and a central, common goal

#### Providers of technology and services to the pharmaceutical industry

- The majority of CMOs currently do not support CM facilities or technology
- Technology providers are starting to provide technologies, with drug product systems further advanced than API manufacture

### PRE-COMPETITIVE COLLABORATION

- FDA and EMA are strong supporters of future manufacturing technologies such as such as CM, however, a standard approach to process approval has yet to be defined
- Other regulatory bodies are yet to provide strong positions on these new technologies, often providing a challenge during inspections and approvals

#### Approaching the Regulators

- Approaching the regulators with a defined strategy to gain regulatory sign-off on processes and facilities will set the industry gold-standard
- Developing this as a collaboration of PharmaCo will demonstrate the industry drive to change, as well as reducing the cost of engaging

#### Approaching technology providers

- Collaborations have driven the development and uptake of areas of CM to date
- Continuing to work in groups such as with CMAC creates the demand required for technology providers to provide solutions that work for the entire industry



# Learning from the extensive published information

Being an area of rapid change and cutting edge development, there is a significant quantity of academic material relating to many of the existing CM facilities. Whether CMAC is involved, or another academic institute, there is significant learning to be taken from the efforts of others.

## CMAC – Connecting academic institutes with industry expertise

CMAC aims to transform the current manufacturing process into the medicine supply chain of the future. Bringing together academic institutes, technology providers and global pharmaceutical companies, they deliver large quantities of academic understanding, in an environment that makes the produced insight relatable and applicable to the companies that need it.

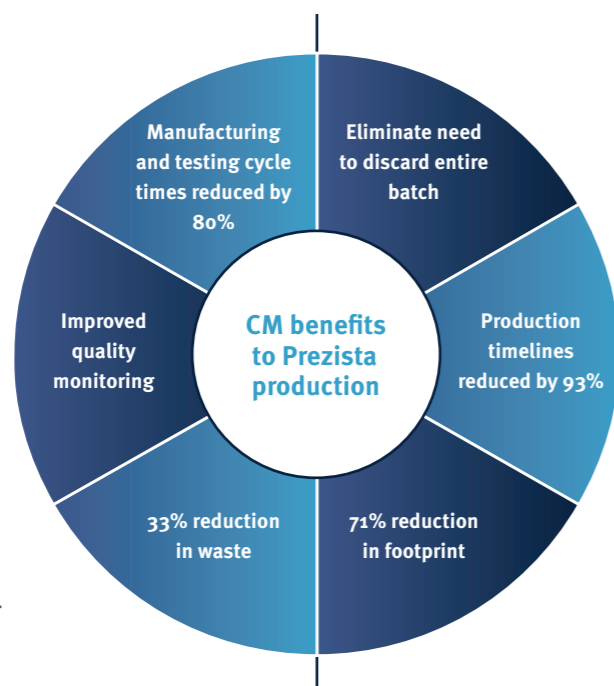
## Janssen and Prezista

In 2016, after 5 years working in conjunction with Rutgers University's Centre for Structured Organic Particulate Systems (C-SOPS) and the University of Puerto Rico, Janssen was granted approval by the FDA to produce 600mg tablets of the HIV drug Prezista (Darunavir) on a continuous production line at its plant in Puerto Rico. Janssen announced that they aim to produce 70% of their highest volume products with CM.

Being first to market is important. Each week a blockbuster drug is delayed translates to a \$20m USD loss in revenue. Furthermore, being first for large PharmaCos can translate into an 11 point advantage. The cost of new products launching between 2019 and 2023 are expected to reach \$45.8bn USD (+5.5% from previous period), CM can bring forward release times and enhance return on investment.

Real-time data capture on critical processes can develop complex multivariate models and automatically compensate for unexpected process disturbances. Process data generated during the development phase will be used to 'teach' process control systems to respond to process disturbances even before commercial manufacturing begins.

An estimated \$50bn USD is lost as waste each year in the US alone due to inefficiencies of batch production. PharmaCos can no longer afford to accept these losses as they face rising costs (R&D up almost 100% in the past 10 years) and an outcome-based model.



Key intermediates for API production can cost \$000's/kg, CM can halt production which could save millions from discarded batches due to impurities.

Specialised therapies will continue to be an increasing focus (spend to reach up to \$505 billion USD by 2023) which will require agile manufacturing capabilities to cope with a segmented customer base. Reduced timelines will allow PharmaCos to switch between short term market demands.

Other investments such as Amgen's Singapore facility (75% reduction) resulted in an \$800 million USD saving when compared to its batch production (same output) in Rhode Island. CM reduces the risk exposure to investments in an increasingly challenging time for R&D productivity.

Working with academic institutes enables pre-competitive development, resulting in faster uptake and clear unified standards that will result in solutions that are more widely applicable, and more widely acceptable in the industry.

# Leveraging CM to bring commercial advantages

Commercial strategy will strongly benefit from the flexibility and speed of continuous manufacturing. From competitive pricing to forecasting, the additional revenue and competitive advantage generated will help capture further market share and increase the likelihood of being first to market.



## Launch

Launch forecasts are typically very inaccurate, a significant underestimate can prevent launch in all markets. CM enables better adaption to market conditions.

## Pricing, Exclusivity and IP

CM delivers benefits in reducing both Operating Expenses (OPEX) and Capital Expenditure (CAPEX). This reduction in costs enables CM adopters to maintain market share at the end of patent life and compete more effectively against generics manufacturers, who have inherently lower fixed cost bases.

The introduction of novel chemistries and processes enabled by the enhanced temporal and spacial processing in CM will enable new IP for new chemistries as well as enabling entirely new product formulations and performance.

The investment (or co-investment with large pharma) in more efficient equipment and ways of working will allow CMOs to differentiate themselves vs competitors, ensuring access to new, more exclusive markets and increase their fundamental skillset. (Additional information via CMAC Tier 1 discussions)



## Marketing

There is prescriber and public demand to have greener, high quality medicines, which can be achieved through continuous manufacturing. Given the public demand, it is foreseeable that it would impact future tenders.



## Stock

The increased security of supply increases trust and could gain preferential positioning in highly competitive categories. Furthermore, it protects against brand damaging stock outs.

## Technology

More flexible manufacture, and increased data, position the business to take advantage of upcoming technology, such as Digital Twin process design and control, and connected supply chain. This will give key competitive advantage, bringing the industry closer to the standards set in other manufacturing industries.



# CMO strategy

Contract Manufacturing Organisations (CMOs) provide a significant proportion of drug production. Some CMAC Tier 1 members outsource up to 90% of their API manufacture. Currently, there are very few instances of CMOs working in continuous manufacturing.

## Eli Lilly on the front foot with CMOs

One of the leaders in continuous manufacturing is Eli Lilly with a functioning API production facility in Kinsale, Ireland, following several investments in the site. Concentrating on small volume production, around 10-15 kg a day, this site enabled the significant development of internal capability. The next step, therefore, is to bring CMOs on-board to boost the manufacturing capacity and work together towards a fully continuous future<sup>42</sup>. Hence Eli Lilly have been proactive in seeking a CMO partner and conducting site visits. Taking things one step at a time, they are looking for a R&D and hybrid production partner, before moving to a larger scale integrated continuous manufacturing collaboration.

### Own the technology

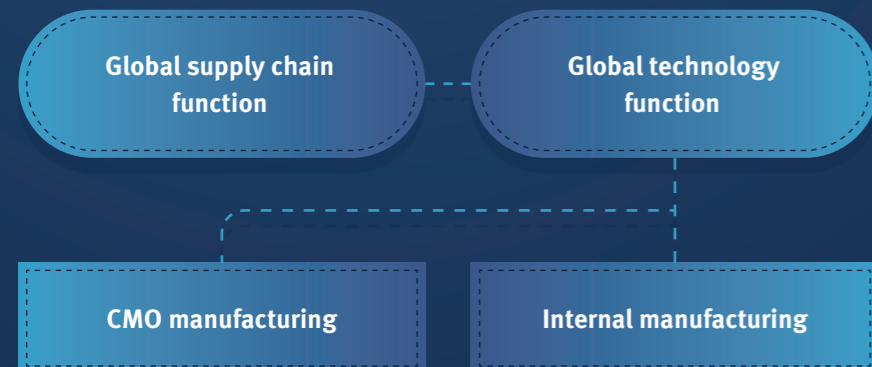
- Develop the technology through the process development teams in-house and retain ownership of the portable technology
- The operation can then be moved to CMOs around the world as and when required, who operate your technology in their facilities
- This will require some collaboration with CMOs to develop Standard Operating Procedures (SOPs) and staff requirements

### Build a partnership

- Partner with a CMO to develop the technology together, with the mutual benefit of owning the technology, whilst guaranteeing the use of the CMO for manufacturing
- There is a risk of pricing power swaying to the existing CMO if no other CMOs develop technology
- Chosen CMO would need international presence to maximise supply chain value

In the event that the technology is developed in-house, it is recommended that the ownership lies in a global function, alongside the supply chain, as demonstrated in the diagram below. This will allow seamless movement of portable skids between both internal and external manufacturing sites without the additional cost of a territory-based system.

## SUGGESTED GLOBAL MANUFACTURING STRUCTURE:



This allows internal manufacturing to be operated in a more similar way to current CMO capability, with the potential to reduce internal operating costs through driving competition and providing more flexibility.

# A new dimension to enhancing R&D agility

## Faster Clinical Trials

Rapidly scale-up Investigational Medicinal Products and repurpose manufacturing. This could allow for new indications and result in a robust pipeline, which delivers value at every phase.

## Location Flexibility

Bring small scale manufacturing closer to the trial sites with MicroFactories.

## Quality Risk Managed

Continuous manufacturing is built on the principles of Quality by Design.

## Agile Scale-Out

MicroFactories can be readily replicated across sites and better understood. Well characterised CM equipment now enables much faster, more reliable scale-up (especially for API) where simply running equipment for longer does not meet the material demand



## Consistent Quality

Quality can be kept consistent throughout the lifecycle of the trial, reassuring clinicians of trial safety.

## Minimal Scale-Ups

For APIs lab kit can be the same scale as for commercial use, especially as drug volumes decrease.

## Design Space Flexibility

Ensuring phase 1 trials can flex to commercial and clinical outcomes, ensuring patients have access to medicines safely and more readily.

## Effective FTE Use

Repurposing FTEs to best utilise their abilities can speed formulation times within a design space.



### New Chemistry

Continuous synthetic chemistry opens up entirely new routes to synthesise molecules including electrochemistry, light catalysed processes as well as extreme temperatures and pressures.



### Effectiveness

Improved yield and purity of APIs.



### Consistency

Early process development and optimization with quality control embedded in the manufacturing.



### Improved Management

Versatility in supporting R&D activities is inherent in CM technologies.



### Efficiency

Managing capacity and balancing drug needs for global clinical trials becomes a reality.

# Identifying CM value in the pipeline

As a drug goes through its development, there comes a moment where a decision needs to be made on the go-forward technology for commercial manufacturing.

## Knowing what to look for

Key attributes for a drug candidate, such as production volume and cost, should be defined early for a potential continuous manufacturing process to maximise the benefit of CM technology.

## Tailoring the product to the technology

Identifying a potential CM candidate as early as possible will allow the product development to tailor the design to the CM process, building in characteristics that will enable the manufacture of the product in an existing or standard facility.

## Decision points through the lifecycle

A go/no-go decision point for selection of manufacturing technologies usually occurs between phase I/II clinical trials. CM, therefore, needs to be embedded in early phase development to be a viable option during development of the process. Many cost benefits can also be realised post-launch where the cost of manufacture is well established and improvements in yield, operational costs, cycle time etc. through application of CM can be readily quantified and a business case more readily generated.

## THE ACQUISITION PIPELINE

- An increasing proportion of a pipeline comes from external acquisition, purchased after the Phase II clinical trial.
- Most of these products are already too far down the development and approval pipeline for the cost of transferring to continuous processing to be justified.
- A clear challenge is therefore driving the uptake of CM to the point where it is more commonplace, even in small single-product businesses.

## REDESIGNING REGULATORY

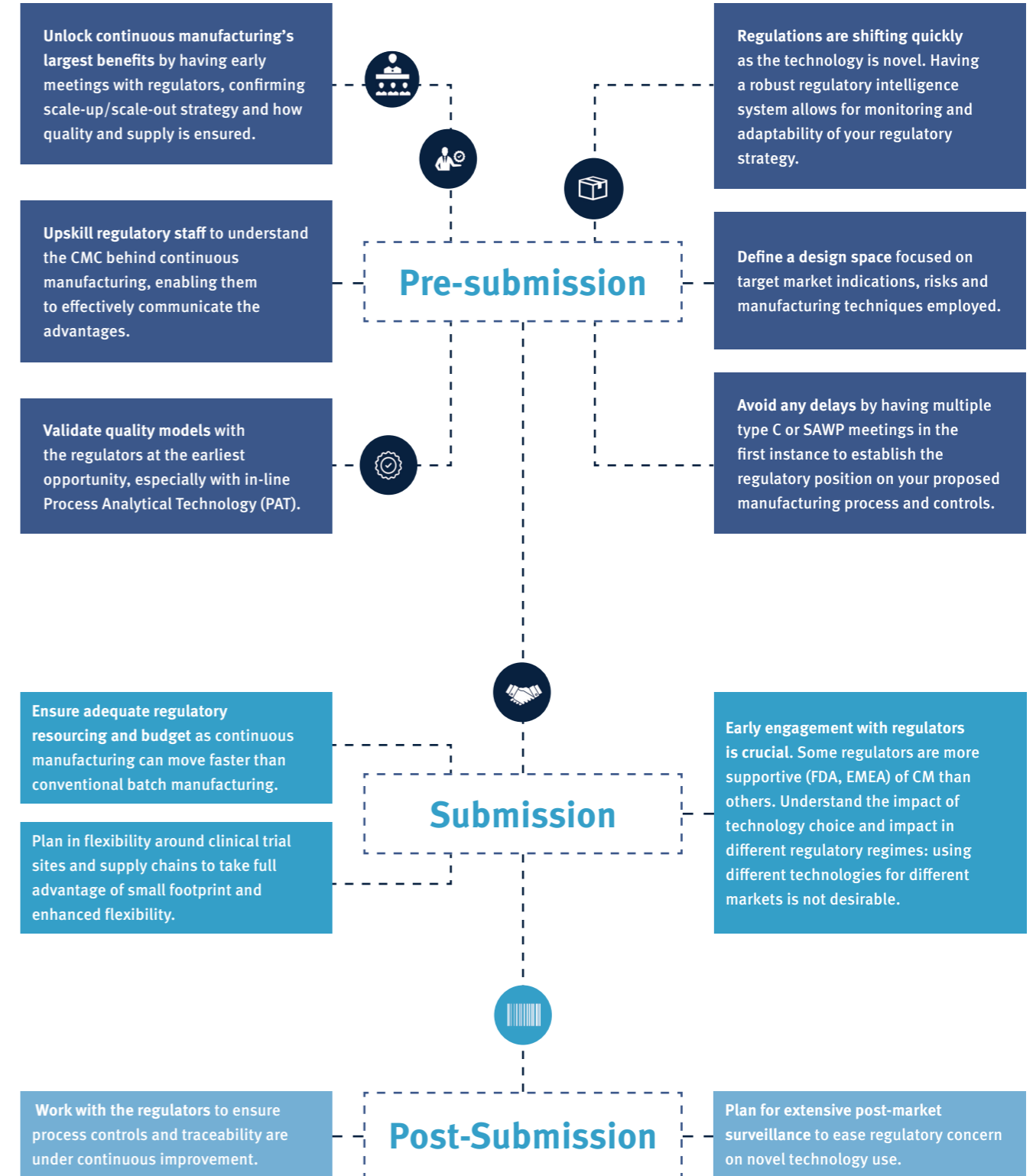
The regulatory burden required to implement a continuous manufacturing line was stated as the main concern, and a significant cost, in the uptake of the technology in the industry:

Regulatory staff will have to undergo <b>upskilling</b> . Early interaction and collaboration with the regulators is essential, with costs being dependent on the competent authority you are interacting with.	Chemistry, Manufacturing and Controls (CMC) documentation will need to fundamentally describe a <b>state of control</b> over the entire CM process; with systems intelligent enough to detect process disturbances in real time.	Validation of equipment particularly with a view on how <b>scalability</b> will be managed.
Due to the continuous nature of manufacturing, <b>material traceability</b> must be clearly established through batch definitions.	Regulators will scrutinise proposed <b>design spaces</b> and workflows to understand interactions between them.	<b>Raw materials</b> need to be clearly understood and managed to avoid variability.

The international regulatory landscape is actively moving towards a more harmonised global strategy. This is best demonstrated through the ICH's development of a new guideline (ICH Q13) on continuous manufacturing due for adoption in 2021. This would in effect facilitate international harmonisation and ultimately reduce barriers to adopting CM technologies. However, international regulatory authorities have widely accepted that the current regulatory environment is compatible and supportive of CM emphasising the need for Quality by Design (QbD).

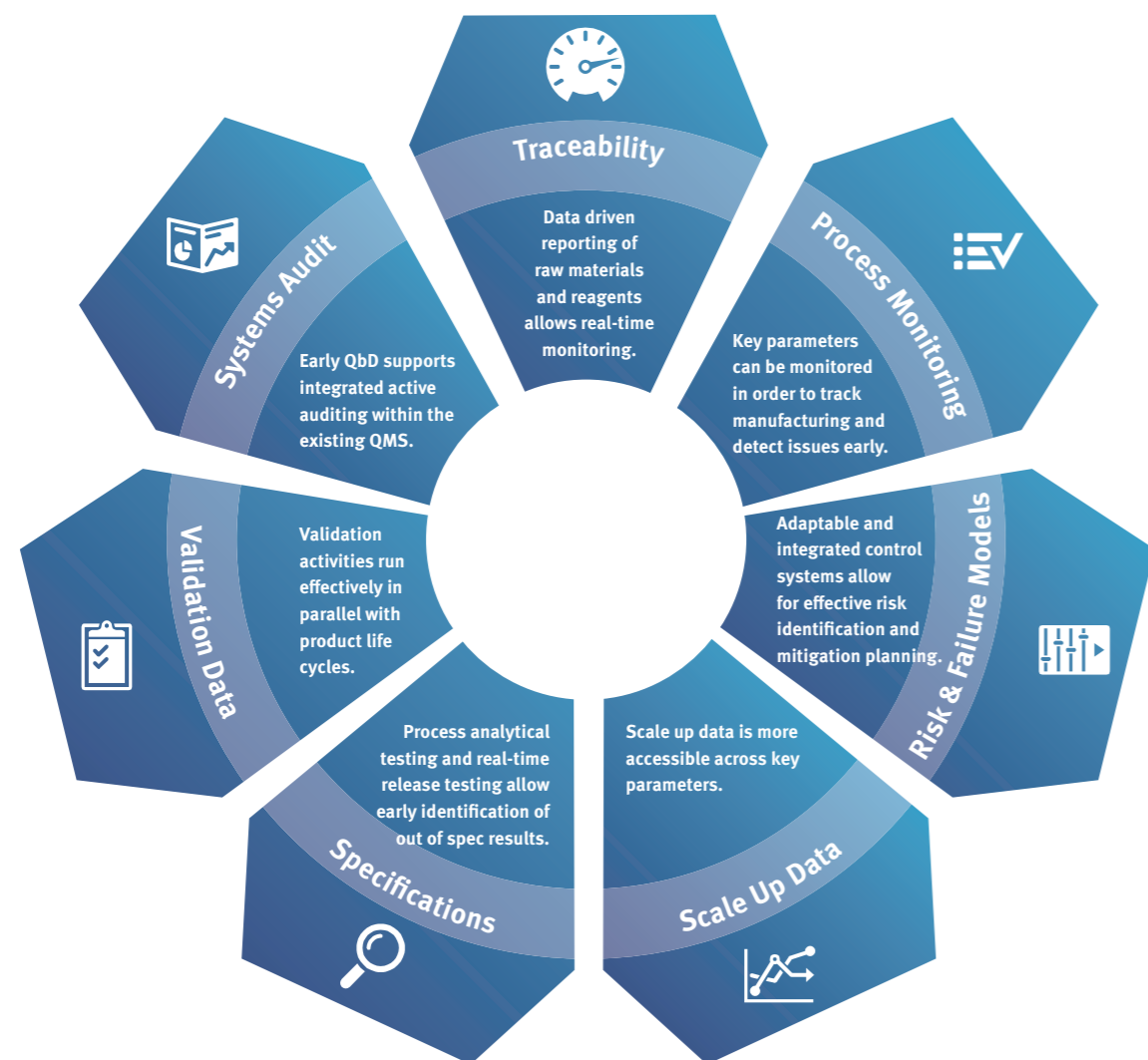
# A regulatory roadmap

Development of a robust regulatory strategy in the first instance will ensure timely approval and exert reassurance to regulatory agencies.



# Enabling and enhancing Quality Management Systems

Real time data provided on a better understood system, that is in a state of control, enables key big data and AI capabilities to a QMS. When this is coupled with the potential to produce more consistent quality product the end-user is significantly benefited, whilst reducing the manufacturing cost.



## Key characteristics of a data-enabled QMS system

- Focuses on product and patient quality, in addition to compliance
- Drives a competitive advantage through speed, reliability, product and data robustness
- Emphasises scientific and operational excellence (building capabilities, frameworks, and designing robust products and processes)
- Focuses the organisation on a culture of excellence and innovation
- Builds end-to-end business processes across the product lifecycle (GxP)

# Defining value from continuous versus batch manufacturing

## OPERATIONAL OUTCOME

## KEY IMPACT METRICS

<b>Competitive Compliance</b> Effective & efficient	<ul style="list-style-type: none"> <li>• OpEx efficiency gains (FTEs/cost savings)</li> <li>• On-time execution rate</li> <li>• Compliance overdue activity</li> <li>• CAPA effectiveness: % of repeat occurrence</li> </ul>
<b>Speed to Market</b> New product launches	<ul style="list-style-type: none"> <li>• On-time completion for regulatory commitments / adherence to plan</li> </ul>
<b>Reliable Supply</b> Clinical, launch & commercial supply	<ul style="list-style-type: none"> <li>• On-time batch acceptance</li> <li>• Reduced batch cycle times</li> <li>• Disposition cycle times, % on-time improved, reduction in % rejected batches</li> </ul>
<b>Robust Products &amp; Data</b> Product & process quality	<ul style="list-style-type: none"> <li>• Right first time batch rate</li> <li>• Yield</li> <li>• Process capability index</li> </ul>
<b>Innovation</b> Design for Excellence	<ul style="list-style-type: none"> <li>• Effectively deploy new technologies to the application of gene and cell therapies</li> </ul>

## Commercial Advantage

## Quantifying the full business benefit

The layers of a business case cover beyond the unit operation comparison. The full value of the change to the manufacturing process can only be realised when investigating both the benefit and the impact of the change of manufacturing technology to the entirety of the pharmaceutical business.

A key consideration also comes when considering the economies of scale. The more continuous manufacturing processes that are in place in the business, the greater the cost saving as the development costs and business impacts are reduced.

Full studies of this impact require significant horizontal coverage across the business, undertaken at a high level and considerate of all aspects of the business operations.

# The impact of tax

There are a number of potential tax implications/opportunities to consider where an industry development leads to material business change. These can include considerations around change management, transfer pricing, IP, patents and value chain analysis.

## Managing the business change

The implementation of CM may impact on the traditional value drivers in the pharmaceutical industry value chain (typically seen as IP, R&D and sales/marketing functions) and cause additional value to be attributed to the manufacturing function (including the design and control thereof). As such, the introduction of CM warrants consideration as to the impact upon where key group value drivers (and therefore the associated profits to be taxed) will/could reside in the future.

Groups will need to be mindful in considering how such a change in value drivers could impact their current tax model/footprint. For example, if the group operates through a centralised business

model, what is the IP, substance around the CM design and control of associated assets and risks that would need to reside in the central hub so as to align the new CM facility to any existing operational and associated tax model?

As well as evaluating any tax conversion issues and tax compliance requirements, if adopting a new CM operation, groups may also give consideration as to whether it represents a commercial catalyst driving a need to evaluate the wider group operating footprint. This business change may be a trigger for a wider restructuring exercise which may be beneficial in light of the evolving tax landscape and enable the group to identify a more efficient, aligned, compliant and robust operating and tax model.

## Tax R&D Incentives

Implementation of CM could entitle taxpayers to incentives which are available in many territories (e.g. R&D tax credits in the UK), as manufacturing improvement projects can qualify as development. Where a CM line is used as part of the development process, further tax incentives can potentially be leveraged with respect to the capital investment.

## Local Territory Taxation Rights

The relevant arms length profits associated with the operation of the CM facility will typically be subject to tax in the location in which it is situated. Accordingly, the tax environment of any territory in which manufacturing takes place should be considered, including; prevailing corporation tax rates, access to tax incentives, employment taxes, tax authority landscape and other key taxes.

## Modular Flexibility

Modular flexibility may result in more frequent transfers of manufacturing lines between territories. Transfers of assets and/or value between territories can have tax implications and it is therefore important to monitor any cross-border movements so as to identify and consider any tax conversion issues. The extent of this would be dependent upon the value (and therefore profits) associated with CM.

## Medicines Manufacturing Industry Partnership – Fiscal Environment<sup>44</sup>

The UK is creating a favourable tax environment for innovation and commercialisation in medicine manufacturing, with a significant range of tax benefits across the drug development process, in an attempt to compete with the likes of Ireland, Switzerland and Singapore.

## Key tax takeaways

- Key business change presents an opportunity for the re-evaluation of the business' operating model.
- The business change needs to be managed in a focused and coordinated manner from an operating model perspective to ensure that legacy models are appropriately maintained / new models are established appropriately.
- Groups should consider the implication CM may have on their value chain and distribution of system profits.
- Groups could benefit from tax incentives if this technological advancement is adopted.
- Group governance has to evolve to ensure that no undetected tax liabilities are arising as a result of modular flexibility.

# Legal opportunity

The new approaches to contract manufacturing with continuous technology offers novel approaches to relationships with external organisations, maximising the value of data and minimising the expense of manufacturing.

On-line, large amounts of data coming from the manufacturing process can enable a data-based approach to contracts, with key performance metrics coming from the manufacturing line that can be built into contracts to ensure quality product at all times from a CMO.

Exclusivity in a relationship with a CMO could provide competitive advantage for both the business and the CMO.

## ENHANCED SUSTAINABILITY

Sustainability has been a hot topic internationally with governments tightening regulations concerning emissions and waste. Continuous manufacturing offers the gold manufacturing standard for reducing waste and pushing for local, sustainable manufacturing.

## Savings everywhere

Equipment size and factory footprint, as previously discussed, are significantly reduced. With reduced clean room space being utilised cost savings are immediately realised. This saving is increased by the significant reduction in the number of human interventions required between unit operations. In a continuous primary manufacturing system, it would be possible to go from drug synthesis to isolated API ready to be moved to secondary processing without a single human interaction. This has the potential to reduce the number of human-caused quality issues. There is potential to reduce the FTEs required to run an E2E continuous manufacturing site by up to 50%.

Reducing the consumption of energy, while increasing the usage of renewable energy, is crucial as nearly one third of global energy demand and CO<sub>2</sub> emissions are attributable to manufacturing. This requires considering energy efficiency from a more systematic point of view in the design phase of manufacturing equipment.

Continuous manufacturing will inherently, as part of its efficient nature, provide the necessary foundation to enable future sustainability driven manufacturing models.

Along with wider company strategies on sustainability, continuous manufacturing will compliment PharmaCo's existing sustainability strategies of the future.



## Green future policy

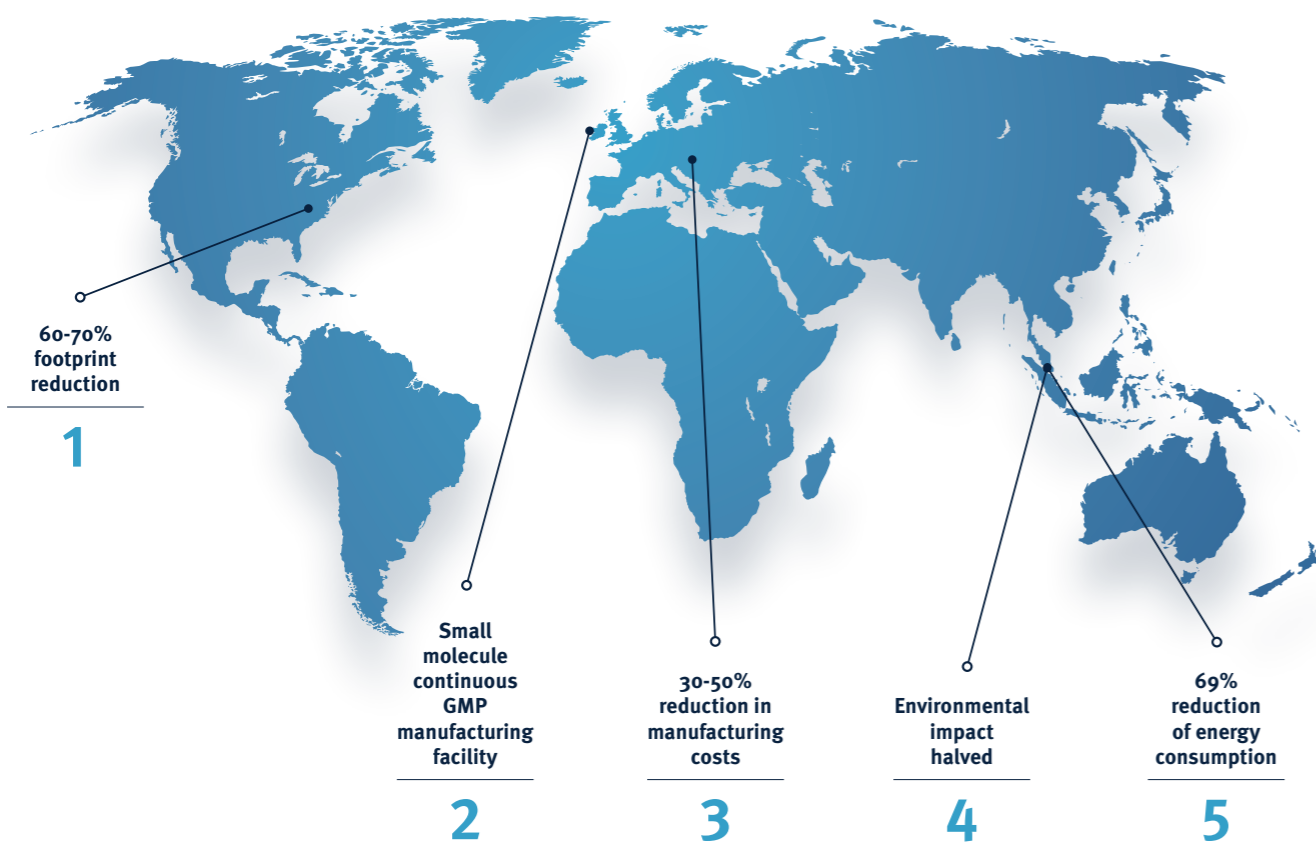
Governments are under pressure to introduce strict legislation in the near future, punishing companies who are not driving a green agenda or moving to more localised manufacturing. Embracing continuous manufacturing gives a clear message that pharma companies are embracing new technologies not only to improve efficiency, but to ensure they remain compliant in a green-focused future.

## Carbon footprint reduction

Approximately, 90% reduction in manufacturing carbon footprint coupled with localised manufacturing dramatically decreases the supply chain footprint. Pharmaceutical companies can take decisive action against climate change and reduce reliance on fossil fuels – getting one step closer to energy independence.

# Examples of CM from around the world

Businesses around the world are starting to invest in continuous manufacturing sites. These sites are being used to further the understanding of the process of manufacturing products using CM, and best position businesses to take advantage of the rapidly changing manufacturing landscape with a test-bed for innovative technologies.



## 1 PCMM at Pfizer in Connecticut<sup>12</sup>

Stemming from a 2013 collaboration with GEA and G-CON Manufacturing, Pfizer invested in a PCMM (Portable, Continuous, Miniature and Modular) plant in Groton, Connecticut. The site, consisting of prefabricated cleanrooms from G-CON and an OSD continuous manufacturing process train from GEA, was reportedly installed and running in a matter of weeks following delivery, winning the 2016 International Society of Pharmaceutical Engineers' (ISPE) Facility of the Year Award (FOYA), in the Equipment Innovation category.

The reasons for this award were listed as a 60-70% smaller facility footprint, the use of the same facility for development, clinical trials and commercial manufacturing, and the significant reduction in installation and start-up times, a reduction from 2-3 years as standard to around 1 year.

## 2 Eli Lilly in Ireland, Indianapolis and Puerto Rico<sup>46</sup>

In April 2016, Eli Lilly announced a 35 million EUR investment to establish a new facility in Ireland with a focus on the continuous manufacturing of its APIs.

The Lilly System is a semi-integrated Direct Compression Continuous Processing Platform that includes highly accurate contained powder feed, blending and tablet compression. A unique and innovative lift system supports the main process train allowing for ease of access, cleaning and change over. Eli Lilly won the 2017 ISPE FOYA for applying this system in both their Indianapolis and Puerto Rico facilities.

## 3 Novartis in Basel<sup>33,47,48</sup>

Novartis have had a longstanding partnership with MIT involving a 3,200 sq ft facility to develop new equipment and ideas. The partnership resulted in Novartis investing in a commercial facility in Basel as part of Novartis' 1 billion USD investment in improving its manufacturing technology capabilities. Novartis recognise the potential to reduce manufacturing costs by 30-50% and manufacturing times by 90%.

## GSK in Singapore<sup>23</sup>

In July 2019, GSK opened a continuous manufacturing site in Singapore, a legacy investment of former CEO Sir Andrew Witty. This site consists of two continuous manufacturing facilities, and the expansion of another facility, with a total reported cost of 95 million USD.

One of these sites is part of an API manufacturing pilot plant that will be used to develop API for clinical trials. The other expansions will allow them to ramp up the production of API for HIV medicines, such as Dolutegravir.

When asked the reasons for the investment, Witty stated he expected smaller facilities, with improved capacity that would cut costs and environmental impact by about 50%.

## Amgen in Singapore<sup>21</sup>

In 2014, Amgen opened a 200 million USD next-generation biomanufacturing facility incorporating innovative to-date techniques and a continuous purification system.

## 5

Due to its modular design, the plant has a 75% smaller footprint and has a reduced energy consumption of 69%. By adopting single-use equipment like bioreactors the facility has managed to reduce water consumption by 45% and reduced cleaning surfaces by over 95%.

## Growing investment

This is just a snapshot of the facilities around the world where information has been openly publicised on the benefits of investing in continuous manufacturing facilities. There are countless smaller facilities, or manufacturing lines containing continuous unit operations as more areas of the industry start investing in flow technology.

## LONG TERM FUTURE

The emergence of continuous manufacturing technologies offers pharmaceutical companies opportunities to be part of the Industry 4.0 paradigm shift. As process understanding matures and regulators get to grips with CM concepts, its place within pharma manufacturing will be assured.

Real value can be identified in daisy-chaining unit operations together, with the long-term goal of development of a truly end-to-end manufacturing line, with E2E process control, online process analytics and quality assurance. A sophisticated Digital Twin aligned to the process will go some way to enabling this future.

In the ever more global and highly competitive market, embedding CM abilities and skills within the existing PharmaCo business strategy could be the difference between surviving and flourishing in the future.

# Implementing CM in your business

The transition from batch to CM will be a paradigm shift for your organisation and change management will be critical to its success: 70% of all change initiatives fail. Of the 30% that succeed, only 10% of these change programmes achieve all the benefits set out at the beginning. There is a strong correlation between change management and this success, as well as other elements of program management.

## WHAT NEEDS TO CHANGE

## CHANGE IMPACT

Technical	<ul style="list-style-type: none"> <li>Fully optimised and trained staff profile</li> <li>Routine application of digital design through a combination of first-principle and data driven models</li> <li>Reduction in manufacturing waste and consistent quality</li> <li>Upskilling and equipment availability across both internal and external supply chains</li> </ul>	<ul style="list-style-type: none"> <li>Quality product produced consistently at a lower cost</li> <li>Faster tech transfer, scale-up and process development coupled with accelerated clinical strategies will reduce time-to-launch</li> <li>Real-time quality assurance</li> </ul>
Supply Chain	<ul style="list-style-type: none"> <li>Closer match to market demand reducing chance of stock-out or shelf-life waste</li> <li>Ultimate flexibility in supply</li> </ul>	<ul style="list-style-type: none"> <li>Lower cost of manufacture through increased flexibility</li> <li>Increased supply chain complexity for high reward</li> </ul>
Regulatory	<ul style="list-style-type: none"> <li>Fully enabled Regulatory Inventory Management system</li> <li>Data driven regulatory strategy</li> <li>More interaction with regulators</li> </ul>	<ul style="list-style-type: none"> <li>Coordinated regulatory data</li> <li>Improved go-to-market times</li> <li>Rapid and effective regulatory response timings</li> <li>Enhanced international launch</li> </ul>
R&D	<ul style="list-style-type: none"> <li>Early adoption of new manufacturing processes</li> <li>Opportunity to review and improve existing projects</li> </ul>	<ul style="list-style-type: none"> <li>Increased data production, enabling Digital Twin process and product development</li> <li>Significant SOP changes</li> </ul>

## WHERE TO FIND THAT INITIAL VALUE CASE

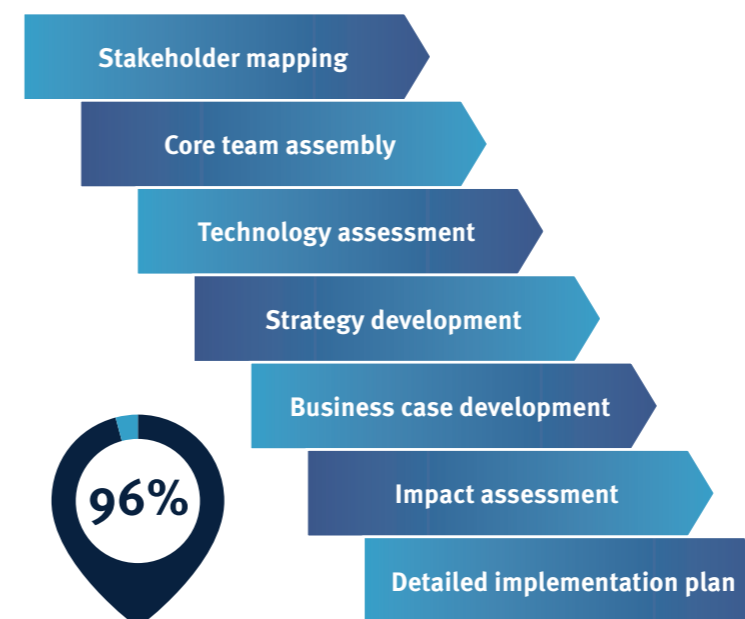
The key to implementing continuous manufacturing successfully is understanding where the change in technology will have the most value for a business:

Targeting implementation on new molecules will maximise the potential benefits, allowing reduced development costs into the business case and eliminating the duplication of regulatory effort.

This does not mean that there is no value in replacing existing batch processes with continuous facilities. The cost burden is higher, however in some cases the potential benefit might still provide a business case.

As the technology becomes more established, the cost of implementing a CM process will reduce, and a wider proportion of your portfolio will become viable candidates for changing manufacturing process.

## ROADMAP TO SUCCESS



Correlation between effective change management and achieving the project objectives is almost 1:1

Strong leadership and a single vision are required to achieve any significant goal.

As the industry changes extensively over the coming years, with the implementation of Industry 4.0 and other technology advances, continuous manufacturing will become just another step change to providing a better service to the end user.

The change requirement to fully unlock the potential benefits of CM in a business is extensive. Far more than a technology implementation in your manufacturing space, the breadth of

change will require detailed planning and a phased roll-out.

We believe that, in the majority of cases, the benefits far outweigh these implementation challenges for CM. Investing and investigating is the next step to delivering benefits to the patient and to your business in the short term, whilst simultaneously aligning with the industry trends of the next 20 years.

## KEY CONSIDERATIONS TO MAXIMISE VALUE

### Making the most of tax

Effectively using corporate structures, coupled with the flexibility enabled by CM, Pharma companies and CMOs can enjoy highly optimised tax structures which takes advantage from the new manufacturing technologies.

### Enabling your CMO network

CMOs bring vital flexibility to the manufacturing strategy. Innovative continuous leasing models protects manufacturing IP investment from the pharma companies while utilising expertise and flexibility of CMOs to deliver consistent high quality products anywhere in the world.

### New approach to regulatory

Every project should be underpinned by a CM focused international regulatory strategy, aligned to the commercial and manufacturing strategy. Effective utilisation of Regulatory Information Management (RIM) systems enables regulatory truth, rapid reactive and proactive regulatory teams and a lean culture.

### Internal optimisation

The CM technology portfolio could be managed from a central function, at the same level as strategic supply chain, whilst treating internal manufacturing capability in the same way as CMOs. This will enable the transfer of technology internally, and the manufacturing management to be seamless.

# References

- Krummradt, H.; Koop, U.; Stoldt, J. Microreactors at Merck, Darmstadt, Germany. *GIT Labor-Fachz.* 1999, 43 (6), 590–592.
- Anderson, N. G. (2012) 'Using continuous processes to increase production', *Organic Process Research and Development*, 16(5), pp. 852–869. doi: 10.1021/op200347k
- Siddique, H., Brown, C., Houson, I. and Florence, A. (2015). Establishment of a Continuous Sonocrystallization Process for Lactose in an Oscillatory Baffled Crystallizer. [online] Doi.org. Available at: <http://doi.org/10.1021/acs.oprd.5b00127>
- Seosamh Harrington, T., Alinaghian, L. and Singh Srail, J. (n.d.). Making the business case for continuous manufacturing in the pharmaceutical industry. [online] Pomsmeetings.org. Available at: <https://www.pomsmeetings.org/confpapers/051/051-0603.pdf>
- Snead, D. R. and Jamison, T. F. (2013) 'End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts', *Chemical Science*, 4(7), pp. 2822–2827. doi: 10.1039/c3sc50859e
- McConnell, J. R.; Hitt, J. E.; Daugs, E. D.; Rey, T. A. *Org. Process Res. Dev.* 2008, 12, 5, 940–945
- Manley, L. and Shi, Z. (2018) 'Characterizing drug product continuous manufacturing residence time distributions of major/minor excipient step changes using near infrared spectroscopy and process parameters', *International Journal of Pharmaceutics*. Elsevier, 551(1–2), pp. 60–66. doi: 10.1016/j.ijpharm.2018.08.059
- Roth, W. J., Almaya, A., Kramer, T. T. and Hofer, J. D. (2017) 'A Demonstration of Mixing Robustness in a Direct Compression Continuous Manufacturing Process', *Journal of Pharmaceutical Sciences*. Elsevier Ltd, 106(5), pp. 1339–1346. doi: 10.1016/j.xphs.2017.01.021
- Niamh Marriott, EMA approves Janssen's Prezista continuous manufacturing line <https://www.europeanpharmaceuticalreview.com/news/62587/ema-continuous-manufacturing/>
- Srai, J. S., Badman, C., Krumme, M., Futran, M. and Johnston, C. (2015) 'Future supply chains enabled by continuous processing-opportunities and challenges May 20-21, 2014 continuous manufacturing symposium', *Journal of Pharmaceutical Sciences*, 104(3), pp. 840–849. doi: 10.1002/jps.24343
- Less is more with advanced technologies in manufacturing <https://www.gsk.com/en-gb/responsibility/environment/carbon/less-is-more-with-advanced-technologies-in-manufacturing/>
- <https://www.businesswire.com/news/home/20151029005733/en/Pfizer-Announces-Collaboration-GSK-Next-Generation-Design-Portable>
- The Evolving State of Continuous Processing in Pharmaceutical API Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations, J. Christopher McWilliams, Ayman D. Allian, Suzanne M. Opalka, Scott A. May, Michel Journet, and Timothy M. Braden, *Organic Process Research & Development* 2018 22 (9), 1143–1166, DOI: 10.1021/acs.oprd.8b00160
- <http://www.rekasinergi.com/global/en/company/stories/industry/pharmaceutical-production-4-0.html>
- ADDoPT project [https://www.addopt.org/downloads/case\\_studies/addopt\\_tswg\\_apc\\_casestudy\\_final.pdf](https://www.addopt.org/downloads/case_studies/addopt_tswg_apc_casestudy_final.pdf)
- CMAC MOPPS project with reduction in Lactose crystallisation time from 16 hour to 5 hours => intensified process(<https://www.cmac.ac.uk/mopps.htm>)
- Cole, K. P., Johnson, M. D., Laurila, M. E. and Stout, J. R. (2017) 'An automated repeating batch with catalyst recycle approach to nitro group hydrogenolysis', *Reaction Chemistry and Engineering*. Royal Society of Chemistry, 2(3), pp. 288–294. doi: 10.1039/c7re00020b
- Johnson, M. D., May, S. A., Calvin, J. R., Remacle, J., Stout, J. R., Diserod, W. D., Zaborenko, N., Haeberle, B. D., Sun, W. M., Miller, M. T. and Brennan, J. (2012) 'Development and scale-up of a continuous, high-pressure, asymmetric hydrogenation reaction, workup, and isolation', *Organic Process Research and Development*. doi: 10.1021/op200362h.
- Hetrick, E. M., Shi, Z., Barnes, L. E., Garrett, A. W., Rupard, R. G., Kramer, T. T., Cooper, T. M., Myers, D. P. and Castle, B. C. (2017) 'Development of Near Infrared Spectroscopy-based Process Monitoring Methodology for Pharmaceutical Continuous Manufacturing Using an Offline Calibration Approach', *Analytical Chemistry*, 89(17), pp. 9175–9183. doi: 10.1021/acs.analchem.7b01907
- Cole, K. P. et al. (2017) 'Kilogram-scale prexasertib monolactate monohydrate synthesis under continuous-flow CGMP conditions', *Science*, 356(6343), pp. 1144–1150. doi: 10.1126/science.aan0745.
- Mire-Sluis, A. (n.d.). [online] Cdn.ymaws.com. Available at: [https://cdn.ymaws.com/www.casss.org/resource/resmgr/BADG\\_Speaker\\_Slides/0216\\_BADG\\_MireSluisTonySlide.pdf](https://cdn.ymaws.com/www.casss.org/resource/resmgr/BADG_Speaker_Slides/0216_BADG_MireSluisTonySlide.pdf)
- Manley, L., Hilden, J., Valero, P. and Kramer, T. (2019) 'Tablet Compression Force as a Process Analytical Technology (PAT): 100% Inspection and Control of Tablet Weight Uniformity', *Journal of Pharmaceutical Sciences*. Elsevier Ltd, 108(1), pp. 485–493. doi: 10.1016/j.xphs.2018.07.004
- Palmer, E. (2019). GSK opens \$95M continuous production operation in Singapore. [online] FiercePharma. Available at: <https://www.fiercepharma.com/manufacturing/gsk-opens-130m-continuous-production-facilities-singapore>
- Hayek, M. (2017). Continuous Manufacturing: Is Pharma Ready? | Accenture. [online] Accenture.com. Available at: <https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready>
- Srai, J. S., Harrington, T., Alinaghian, L. and Phillips, M. (2015) 'Evaluating the potential for the continuous processing of pharmaceutical products-a supply network perspective', *Chemical Engineering and Processing: Process Intensification*. Elsevier B.V., 97, pp. 248–258. doi: 10.1016/j.cep.2015.07.018
- Mascia, S., Heider, P. L., Zhang, H., Lakerveld, R., Benyahia, B., Barton, P. I., Braatz, R. D., Cooney, C. L., Evans, J. M. B., Jamison, T. F., Jensen, K. F., Myerson, A. S. and Trout, B. L. (2013) 'End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation', *Angewandte Chemie - International Edition*, 52(47). doi: 10.1002/anie.201305429.
- Schmidt, A., de Waard, H., Moll, K. P., Kleinebudde, P. and Krumme, M. (2018) 'Simplified end-to-end continuous manufacturing by feeding API suspensions in twin-screw wet granulation', *European Journal of Pharmaceutics and Biopharmaceutics*. Elsevier, 133(October), pp. 224–231. doi: 10.1016/j.ejpb.2018.09.026.
- Polster, C. S., Cole, K. P., Burcham, C. L., Campbell, B. M., Frederick, A. L., Hansen, M. M., Harding, M., Heller, M. R., Miller, M. T., Phillips, J. L., Pollock, P. M. and Zaborenko, N. (2014) 'Pilot-scale continuous production of LY2886721: Amide formation and reactive crystallization', *Organic Process Research and Development*, 18(11), pp. 1295–1309. doi: 10.1021/ops500204z.
- Zhang, H., Lakerveld, R., Heider, P. L., Tao, M., Su, M., Testa, C. J., Dantonio, A. N., Barton, P. I., Braatz, R. D., Trout, B. L., Myerson, A. S., Jensen, K. F. and Evans, J. M. B. (2014) 'Application of continuous crystallization in an integrated continuous pharmaceutical pilot plant', *Crystal Growth and Design*, 14(5), pp. 2148–2157. doi: 10.1021/cg401572h.
- Adamo, A., Beingsner, R. L., Behnam, M., Chen, J., Jamison, T. F., Jensen, K. F., Monballiu, J.-C. M., Myerson, A. S., Revalor, E. M., Snead, D. R., Stelzer, T., Weeranoppanant, N., Wong, S. Y. and Zhang, P. (2016) 'On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system', *Science*, 352(6281), pp. 61–67. doi: 10.1126/science.aaf1337
- Thomson, N. M., Singer, R., Seibert, K. D., Luciani, C. V., Srivastava, S., Kiesman, W. F., Irdam, E. A., Lepore, J. V. and Schenck, L. (2014) 'Case Studies in the Development of Drug Substance Control Strategies', *Organic Process Research and Development*, 19(8), pp. 935–948. doi: 10.1021/acs.oprd.5b00146
- Demonstrated in ReMediES project <https://www.britest.co.uk/remedies/>
- Neil, S. (2017). Pharma Catches on to Continuous Manufacturing | Automation World. [online] Automationworld.com. Available at: <https://www.automationworld.com/article/technologies/dcs/pharma-catches-continuous-manufacturing>
- Shanley, A. (2017). PCMM, The Next Generation. [online] <https://www.pharmtech.com/pcmm-next-generation>
- DiProspero, D. (2018). Continuous OSD Manufacturing - A Product & Patient Perspective. [online] ISPE | International Society for Pharmaceutical Engineering. Available at: <https://ispe.org/pharmaceutical-engineering/ispeak/continuous-osd-manufacturing-product-patient-perspective>
- Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them, May 20-21, 2014 Continuous Symposium, Stephen Byrn, Maricio Futran, Hayden Thomas, Eric Jayjock, Nicola Maron, Robert F. Meyer, Allan S. Myerson, Michael P. Thien, and Bernhardt L. Trout
- GEA ([https://www.gea.com/en/applications/pharma/solid-dosage/solid-dosage\\_continuous-granulation.jsp](https://www.gea.com/en/applications/pharma/solid-dosage/solid-dosage_continuous-granulation.jsp))
- Ferguson, S., Morris, G., Hao, H., Barrett, M. and Glennon, B. (2013) 'Characterization of the anti-solvent batch, plug flow and MSMPR crystallization of benzoic acid', *Chemical Engineering Science*. Elsevier, 104, pp. 44–54. doi: 10.1016/j.ces.2013.09.006
- McGlone, T., Briggs, N. E. B., Clark, C. A., Brown, C. J., Sefcik, J. and Florence, A. J. (2015) 'Oscillatory Flow Reactors (OFRs) for Continuous Manufacturing and Crystallization', *Organic Process Research and Development*, 19(9), pp. 1186–1202. doi: 10.1021/acs.oprd.5b00225.
- Malet-Sanz, L. and Susanne, F. (2012) 'Continuous flow synthesis. a pharma perspective', *Journal of Medicinal Chemistry*, 55(9), pp. 4062–4098. doi: 10.1021/jm2006029.
- <https://www.invite-research.com/research/former-research-projects/f3-factory>
- The Evolving State of Continuous Processing in Pharmaceutical API Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations, J. Christopher McWilliams, Ayman D. Allian, Suzanne M. Opalka, Scott A. May, Michel Journet, and Timothy M. Braden, *Organic Process Research & Development* 2018 22 (9), 1143–1166, DOI: 10.1021/acs.oprd.8b00160
- Zhang, P., Weeranoppanant, N., Thomas, D. A., Tahara, K., Stelzer, T., Russell, M. G., O'Mahony, M., Myerson, A. S., Lin, H., Kelly, L. P., Jensen, K. F., Jamison, T. F., Dai, C., Cui, Y., Briggs, N., Beingsner, R. L. and Adamo, A. (2018) 'Advanced Continuous Flow Platform for On-Demand Pharmaceutical Manufacturing', *Chemistry - A European Journal*, 24(11), pp. 2776–2784. doi: 10.1002/chem.201706004.
- <https://www.abpi.org.uk/medicine-discovery/new-medicines-data/medicines-manufacturing-industry-partnership-mmip/fiscal-environment/>
- Rogers, L. and Jensen, K. (2019). Continuous manufacturing – the Green Chemistry promise?. [online] rsc.org. Available at: <https://pubs.rsc.org/en/content/articlehtml/2019/gc/c9gc00773c#cit170>
- <https://ispe.org/facility-year-awards/winners/2019/process-innovation>
- Dougherty, E. (2018). New drug manufacturing tools change pharma chemistry | Novartis. [online] Novartis. Available at: <https://www.novartis.com/stories/discovery/new-drug-manufacturing-tools-change-pharma-chemistry>
- Palmer, E. (2018). Novartis whacking nearly 2,000 manufacturing jobs to pump up margins. [online] FiercePharma. Available at: <https://www.fiercepharma.com/manufacturing/novartis-whacking-nearly-2-000-manufacturing-jobs-to-pump-up-margins>
- Acevedo, D., Peña, R., Yang, Y., Barton, A., Firth, P. and Nagy, Z. K. (2016) 'Evaluation of mixed suspension mixed product removal crystallization processes coupled with a continuous filtration system', *Chemical Engineering and Processing: Process Intensification*. Elsevier B.V., 108, pp. 212–219. doi: 10.1016/j.cep.2016.08.006.
- Harrington, T. S., Phillips, M. A. and Srai, J. S. (2017) 'Reconfiguring global pharmaceutical value networks through targeted technology interventions', *International Journal of Production Research*. Taylor & Francis, 55(5), pp. 1471–1487. doi: 10.1080/00207543.2016.1221541
- [https://www.interphex.com/\\_novadocuments/461568?v=636578725942800000](https://www.interphex.com/_novadocuments/461568?v=636578725942800000)



The EPSRC Future Manufacturing Research Hub for Continuous Manufacturing and Advanced Crystallisation (CMAC) comprises 7 leading UK universities, 8 global pharmaceutical partners and 15 technology companies. CMAC's goal is to enable the pharmaceutical and chemical industries to deliver high quality products in a more economical, efficient and sustainable manner, by advanced continuous manufacturing technologies. The ambitious programme targets current and future needs by developing digital design and modelling methodologies as well as integrated, flexible and modular end-to-end continuous processing platforms. This approach involves product and process understanding for small molecule manufacturing, to meet the current industry demands for more personalised product performance for patients and consumers.

This document is the overall responsibility of CMAC. PwC has contributed to the contents of this document by developing the contents through a combination of desktop research and stakeholder interviews, and PwC's contribution has been prepared only for CMAC and solely for the purpose and on the terms agreed with CMAC in our agreement dated 07/03/2019. Both CMAC and PwC are entitled to publicly share this document, however neither accepts liability for any party's use of, or reliance upon, the contents of this document.

IN ASSOCIATION WITH



© University of Strathclyde



**CMAC**  
FUTURE MANUFACTURING  
RESEARCH HUB

[www.cmac.ac.uk](http://www.cmac.ac.uk)