Hovione

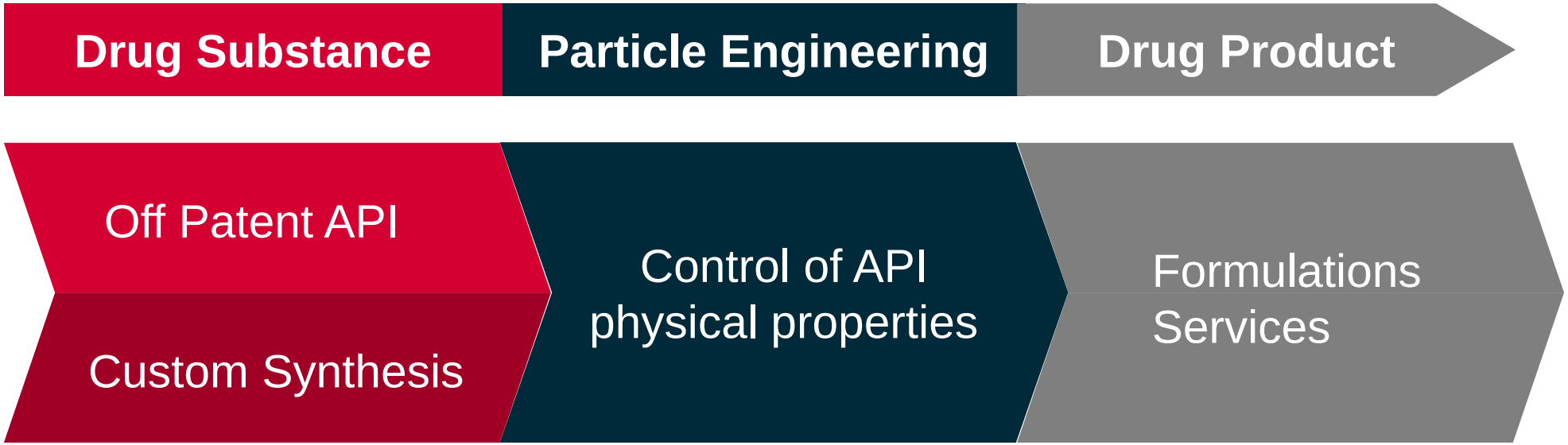
In it for life

Continuous Manufacturing - *continuous or batch?*

Inês Salsinha

14 October 2023

Hovione offers Integrated Development and Manufacturing Capabilities as one of its key value propositions

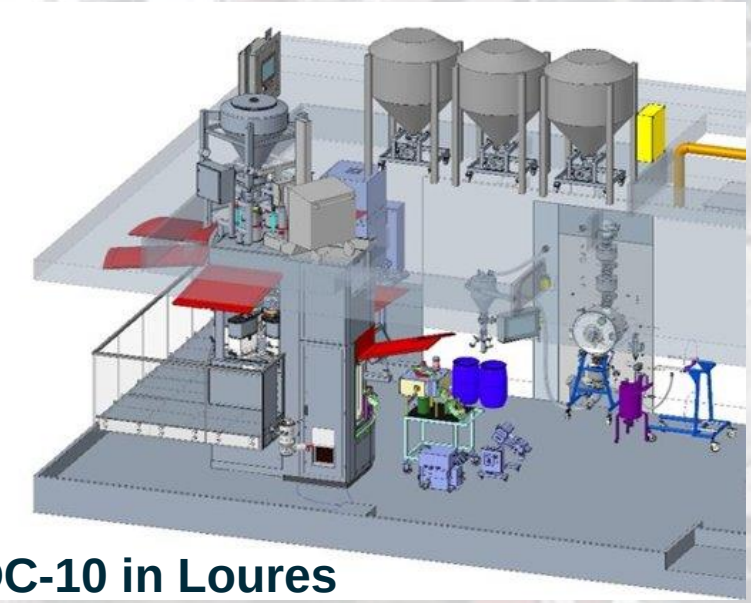


To passionately turn any challenge into a solution, by collaborating with our partners to develop great medicines.

Our Drug Product facility is located at Hovione Loures (Portugal) and back integrates to Drug Substance and Particle Engineering

Our Drug Product facility is located at Hovione Loures (Portugal) and back integrates to Drug Substance and Particle Engineering

- New batch and continuous manufacturing areas (expansion of Drug Product center)
- Batch tableting expansion – Launched in 2021
- Continuous tableting – Launch in 2023/2024
  - Direct compression
  - Twin-screw Wet granulation
- USA unit: FDA approval in 2022



CDC-10 in Loures

What is Continuous Manufacturing?

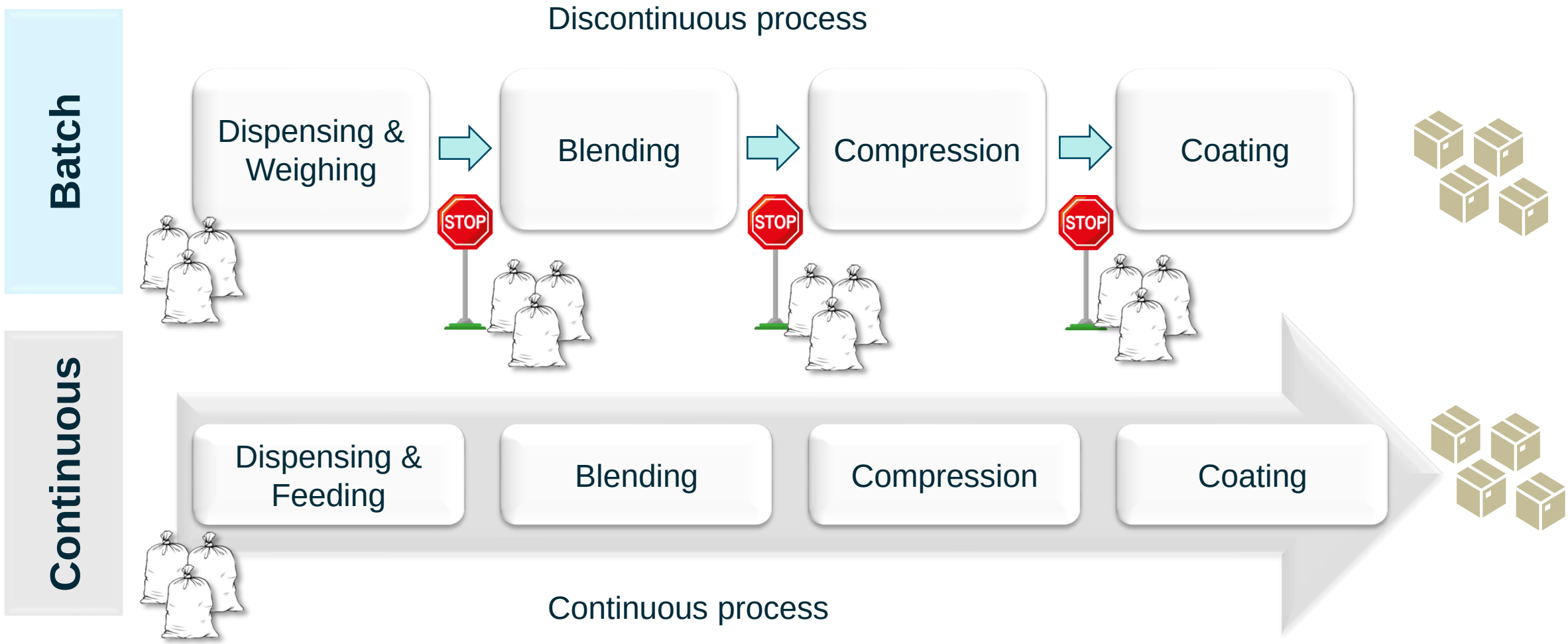
- **CM vs Batch Mode**
- **Batch definition and Control Strategy**
- **What changes and what does not**

Hovione

In it for life

CM vs Batch Mode

Definitions



Batch definition

ICH harmonisation for better health

GuidelineQ13

ICH Consensus Guideline

TABLE OF CONTENTS

QUANTITY OF INPUT MATERIALS

RUN TIME AT A DEFINED FLOW RATE

QUANTITY OF OUTPUT MATERIAL

CAN be defined as a range → Batch size always set prior starting manufacturing activities.

Control Strategy

Main aspects as per ICH Q13

Process Dynamics

*Process dynamics should be characterised to understand how output material quality is impacted by transient events. This characterisation could be done by determining properties such as **residence time distribution (RTD).***

State of Control

*Elements of the control strategy monitor the state of control and, when necessary, **take appropriate actions to maintain control of the process**.*

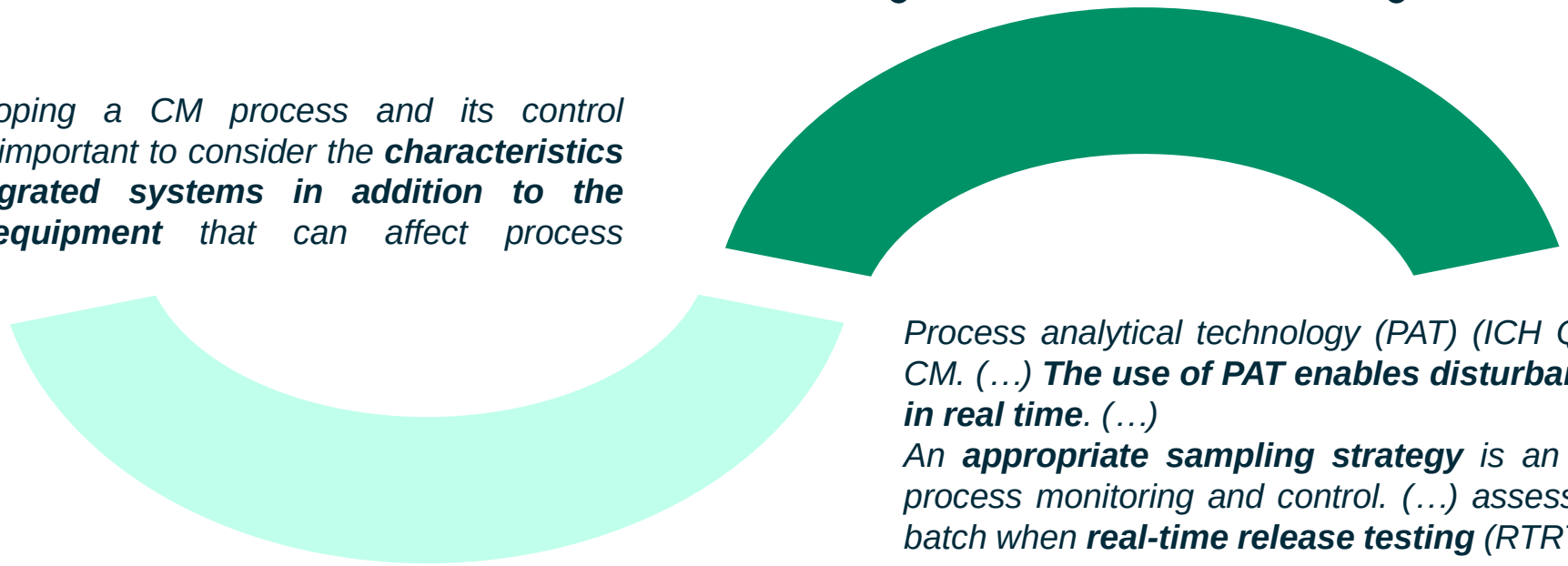
Material Characterization

*Input materials may require **evaluation and control of attributes beyond those typically considered for a material specification** used in batch manufacturing.*

Control Strategy

Main aspects as per ICH Q13

*When developing a CM process and its control strategy, it is important to consider the **characteristics of the integrated systems in addition to the individual equipment** that can affect process performance.*



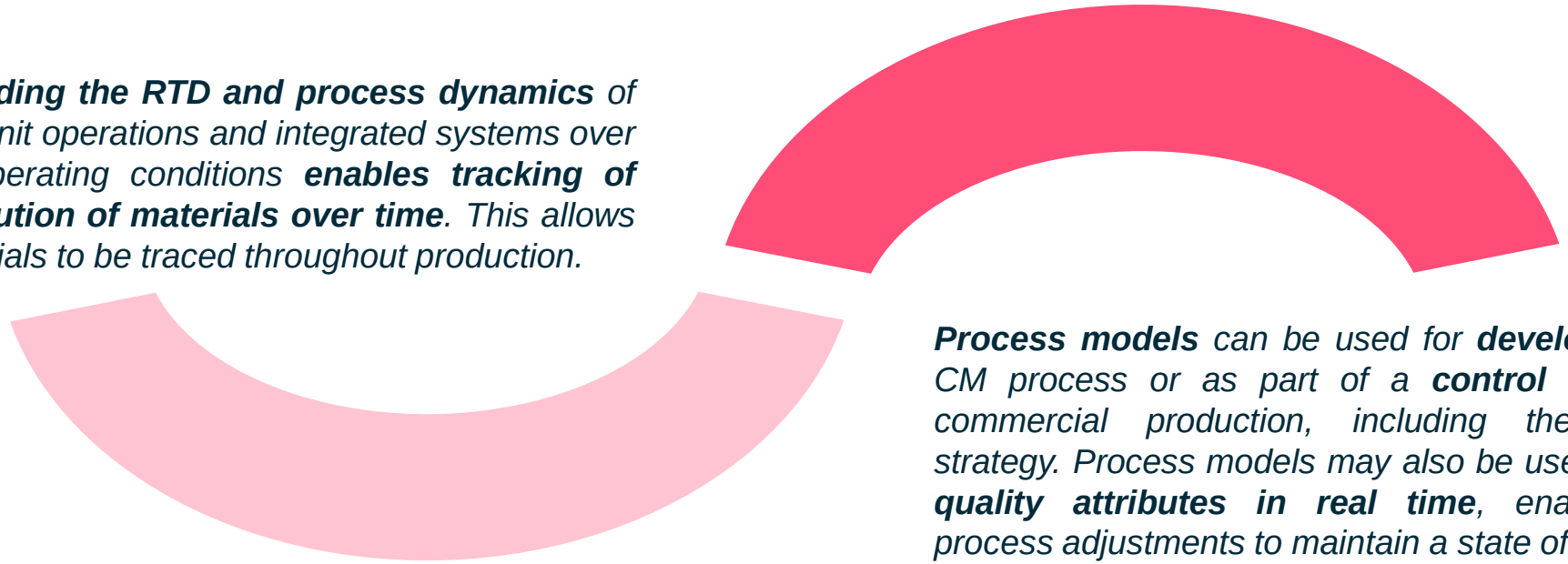
*Process analytical technology (PAT) (ICH Q8) is well-suited for CM. (…) **The use of PAT enables disturbances to be detected in real time**. (…)*
*An **appropriate sampling strategy** is an important aspect of process monitoring and control. (…) assessment of quality of a batch when **real-time release testing** (RTRT) (…).*

Control Strategy

Main aspects as per ICH Q13

Process Models

Understanding the RTD and process dynamics *of individual unit operations and integrated systems over planned operating conditions* ***enables tracking of the distribution of materials over time****. This allows input materials to be traced throughout production.*



Process models *can be used for* ***development*** *of a CM process or as part of a* ***control strategy*** *for commercial production, including the* ***diversion*** *strategy. Process models may also be used to* ***predict quality attributes in real time****, enabling timely process adjustments to maintain a state of control.*

Material Traceability and Diversion

What CHANGES and what does not

Higher focus on Raw Material properties

(e.g. Flowability)

Study of Process Dynamics

Traceability

RMs in final product and Material segregation

Data Size

Handling, Analysis and Review

What changes and what DOES NOT

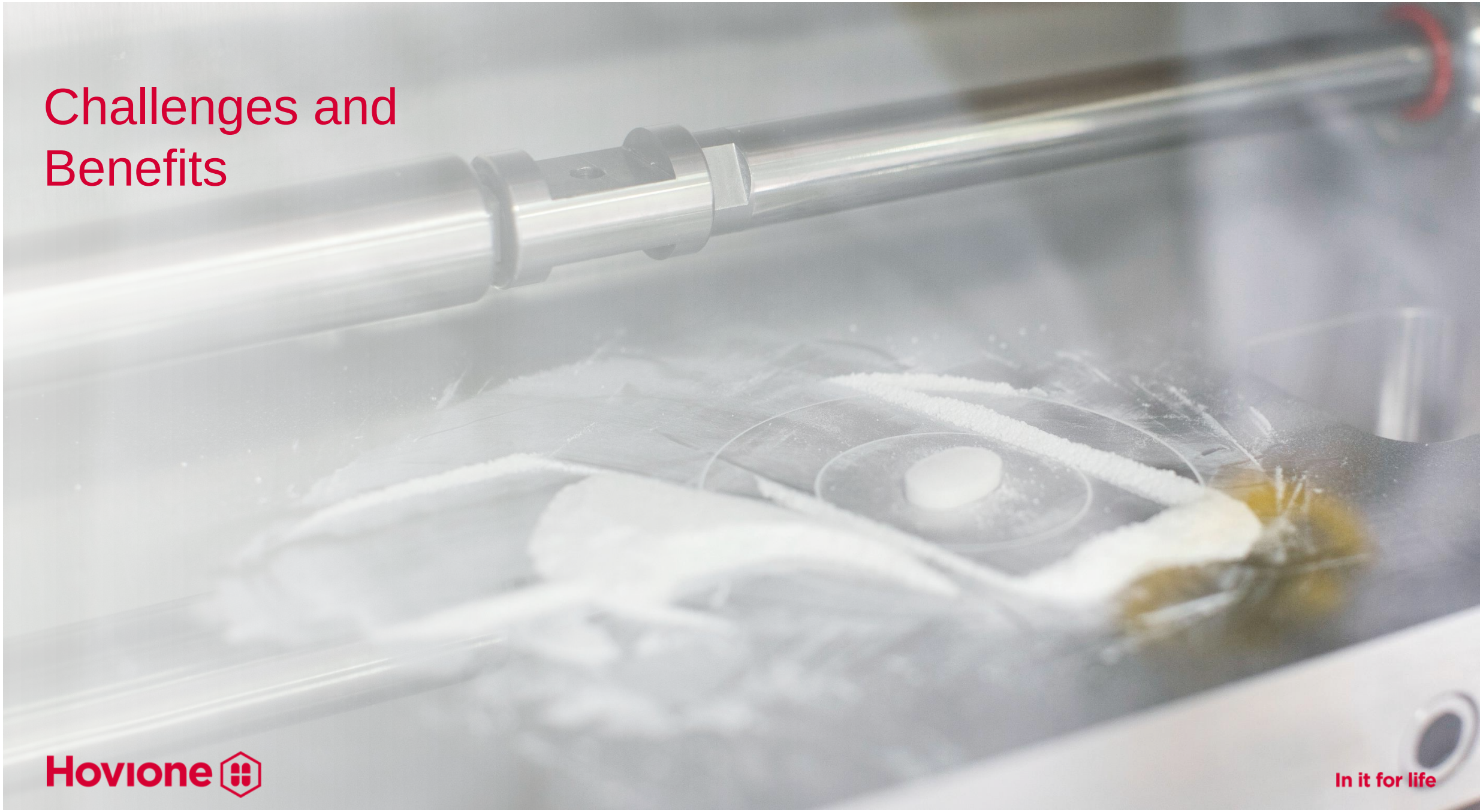
- CM process are bound to the same requirements regarding **cGMP compliance** and the need to demonstrate capacity of reproducible commercial manufacture

- **Control strategy** based on good process understanding, relating raw material properties and process parameters with CQAs

- Controls in place for a CM process should be the result of performing structured **Risk Assessment** and defining risk control strategies – ICH Q9

- **Specifications** are set based on toxicology and clinical data, and from Pharmacopeial standards, regardless of the process being continuous, batch, or with elements of both

Challenges and Benefits



Hovione

In it for life

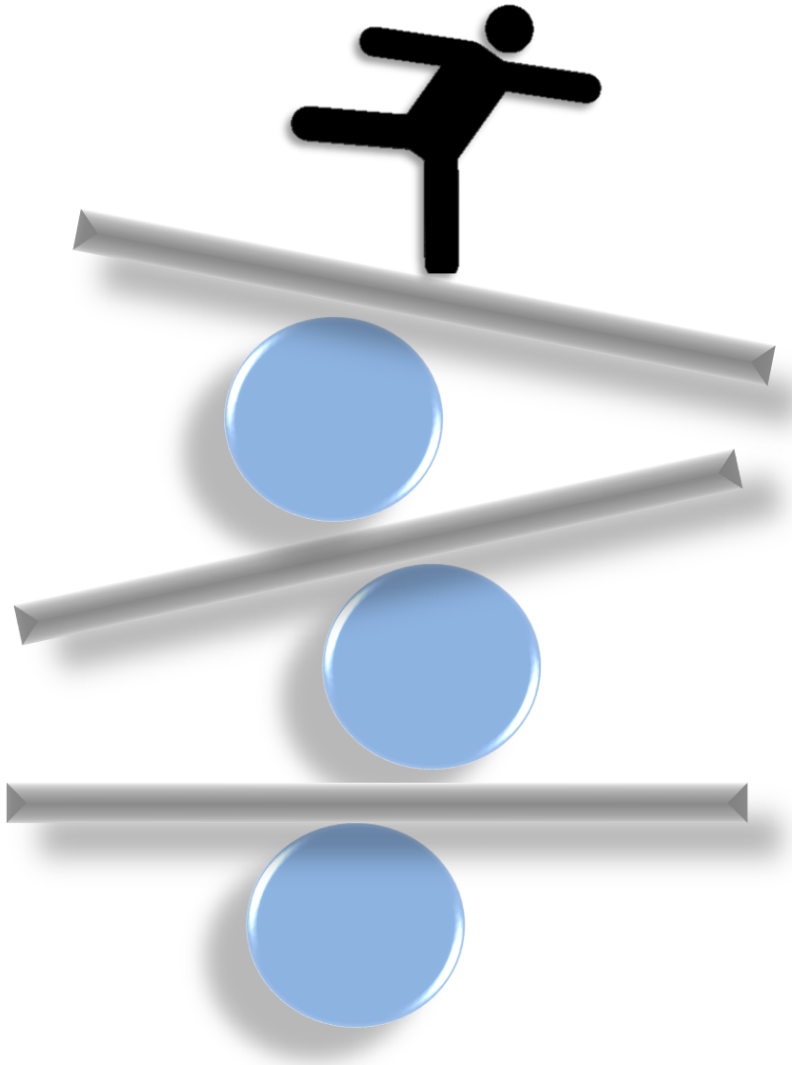
Challenges of implementing CM

Knowledge Management

- Dedicated multidisciplinary teams
- Involvement in forums, partnerships to leverage the knowledge
- Promote participation in training sessions

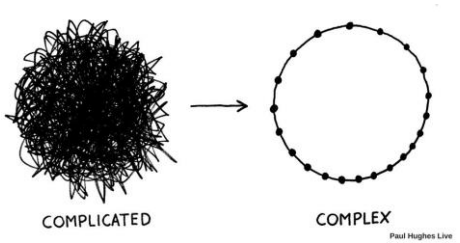
Costs

- Capital investment to upgrade or purchase equipment
- Higher investment during initial implementation phase
- Significant cleaning and setup time during changeover



Complexity and Standardization

- Suitable for different processes: Direct Compression, Dry Granulation, Wet Granulation – fully continuous or semi
- Lack of standard equipment design and software – multiple suppliers
- Several PAT tool
- Definition of Control Strategy



Benefits

- Eco friendlier approach & Smaller inventory
- Less manual handling
- Agile manufacturing to provide supply flexibility
- Reduced processing times and Possibility of performing RTRT
- Drive efficient development and speed to market with limited API

Benefits throughout project lifecycle

Development

- More efficient and with less API
- Reduced processing times
- Smaller Inventories

Validation

- More efficient, same scale as development
- Flexibility to increase batch size → run longer
- Reduced processing times and RTRT as possibility

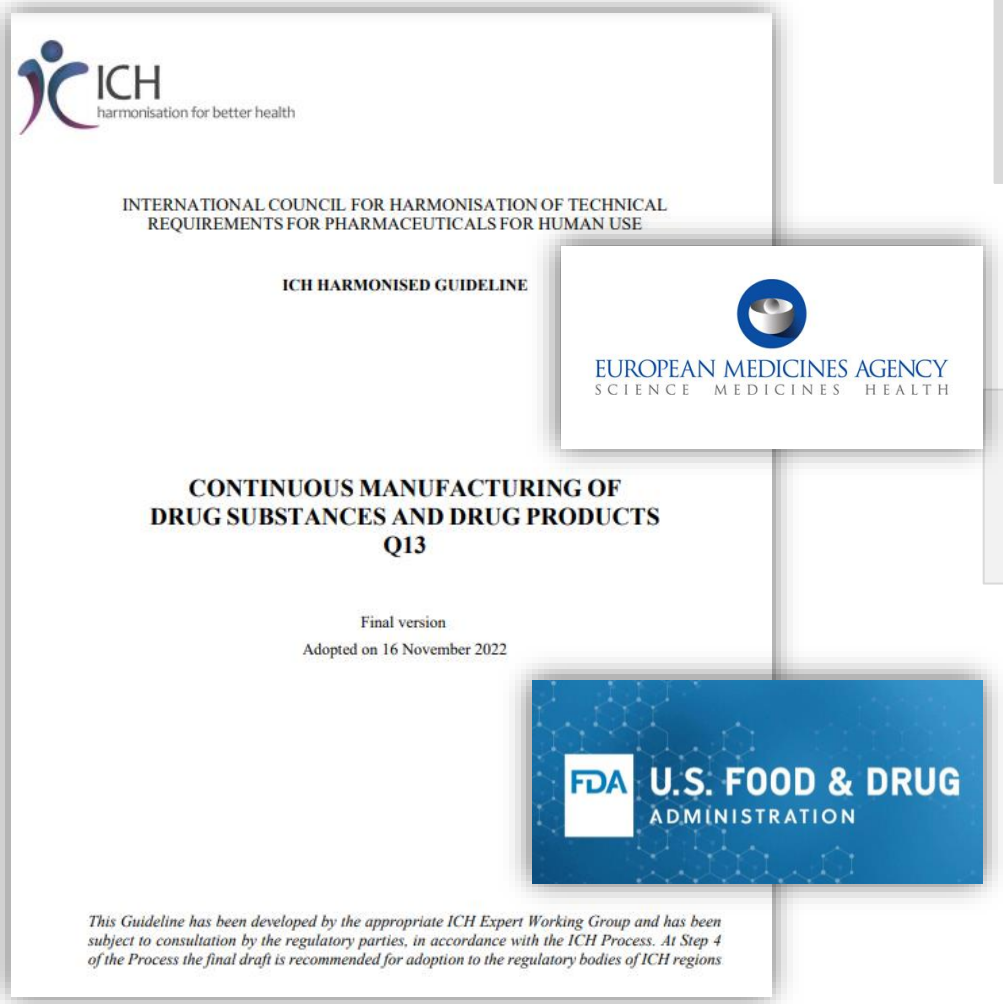
Commercial

More flexibility and robustness, with less costs

Regulatory Landscape

- **FDA and EMA position**
- **ICH Guideline**

Regulatory Landscape



Authorities are supporting and enabling the use of CM, as they acknowledge the potential benefits.

FDA developed a program (ETP) to help industry on advancing and implementing emerging technologies.

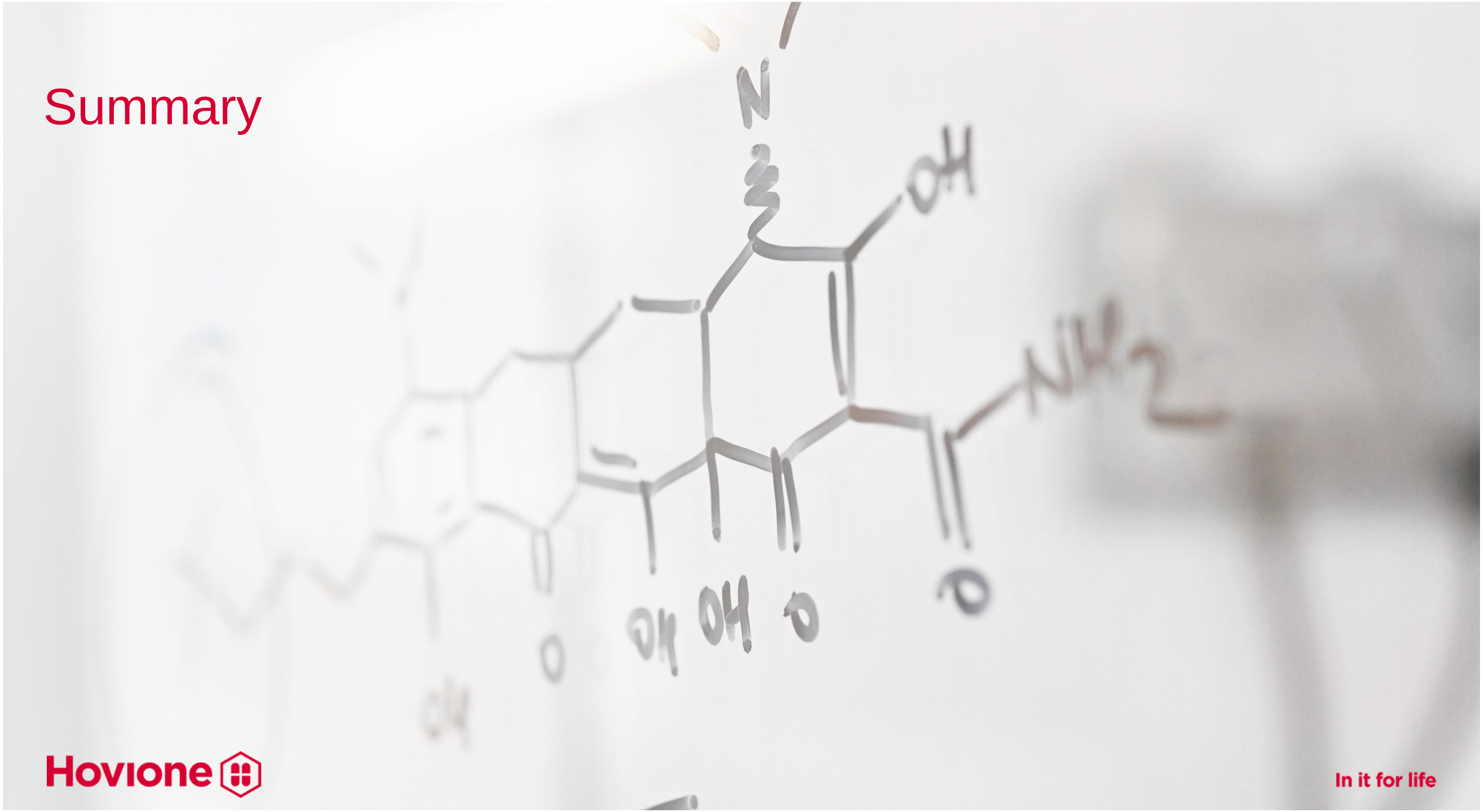
Both EMA and FDA have adopted the ICH Q13 Guideline

Use science- and risk-based approaches, recommending early and frequent discussions with FDA agency.

<u>Regulatory requirements in terms of the quality of the products remain the same as in batch manufacturing.</u>

Note: Over 10 products approved across the world;

Summary

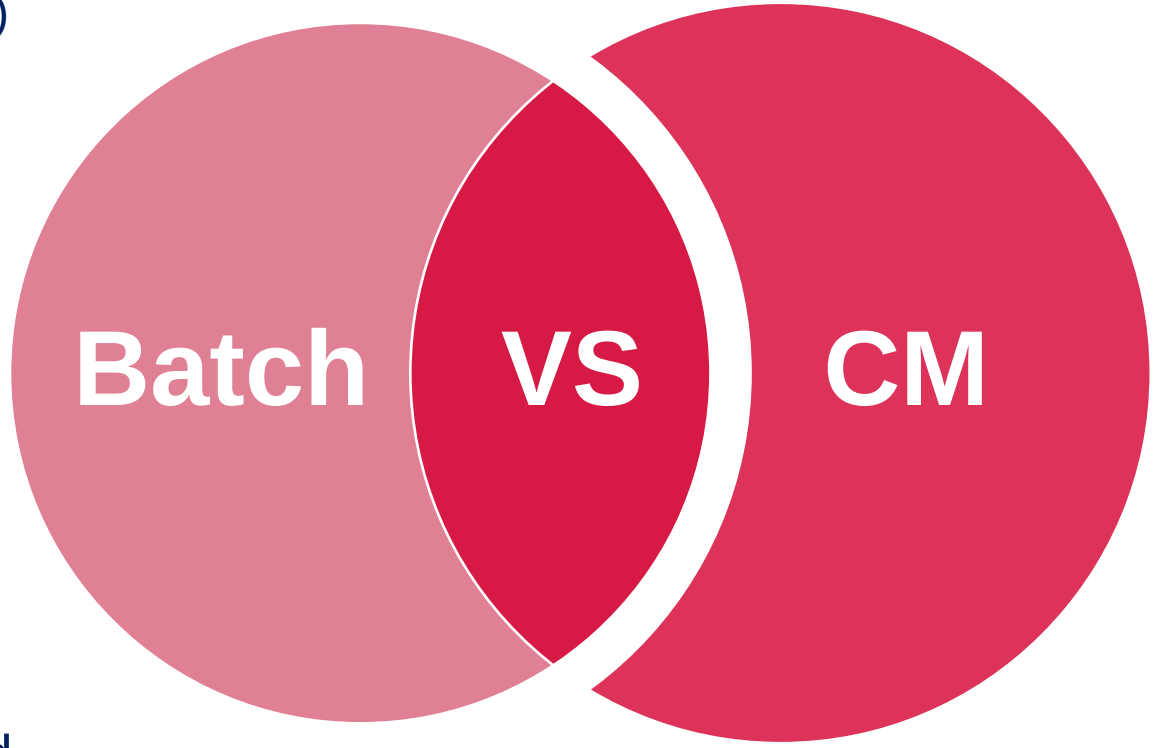


Hovione

In it for life

Summary

- Intermediate stops (longer batches)
- Standard controls
- Setup less expensive
- Well established



- Continuous (shorter run time)
- PAT tools, Process models
- Long term reduces costs and increases efficiency
- Supported by the Authorities

Any Questions?

Inês Salsinha, Senior QA Specialist
isalsinha@Hovione.com

www.hovione.com

Hovione

In it for life

Thank you
for your attention

Hovione

In it for life