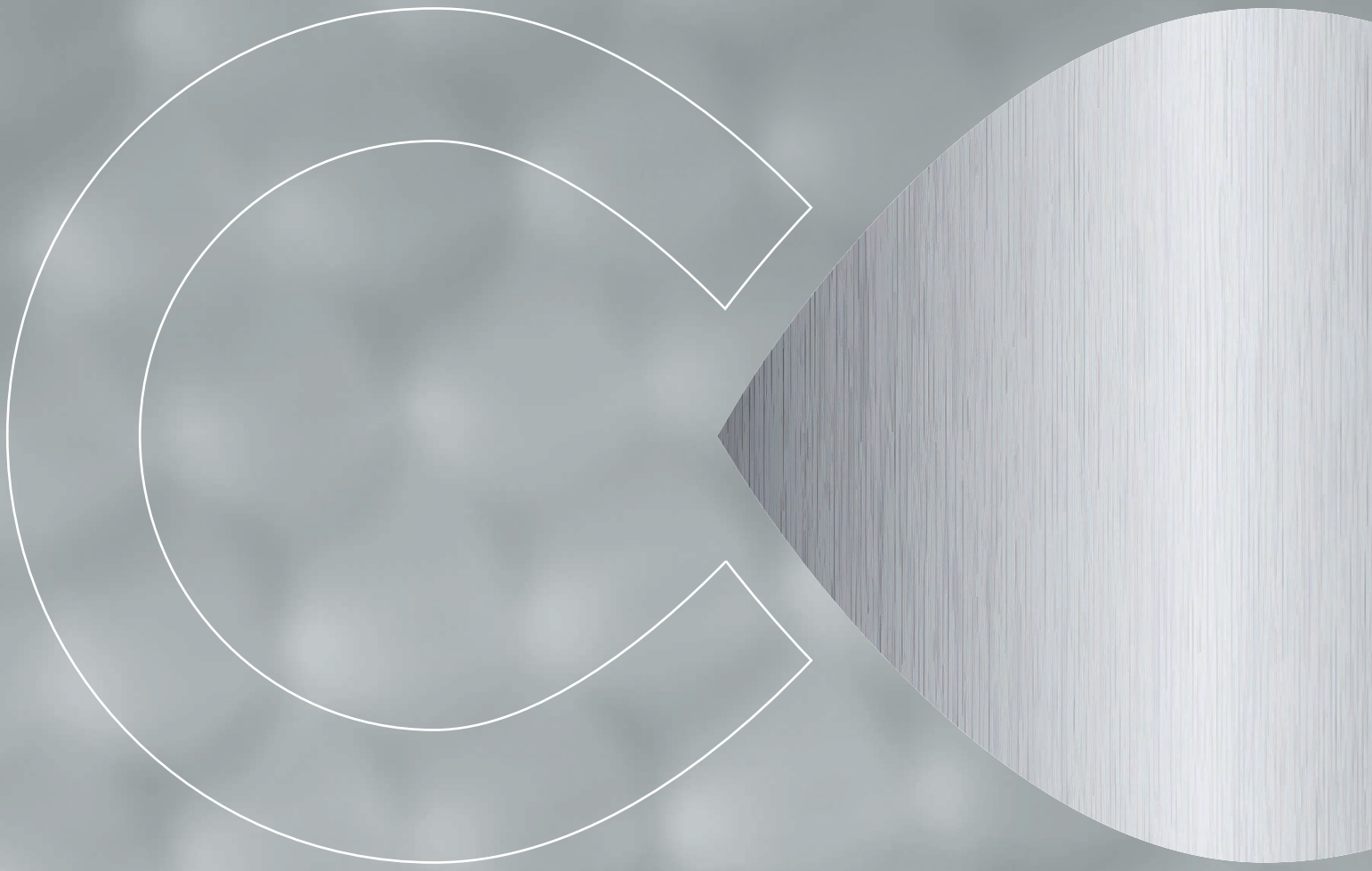
THE CONTINUOUS BOOK



IMA ACTIVE
Solid Dose Solutions


CONTINUOUS
MANUFACTURING

CONTINUOUS MANUFACTURING

TO BELIEVE IN

As the pharmaceutical industry endeavours to enhance its safety and quality standards, while achieving greater production agility and sustainability, there is clearly a growing interest in Continuous Manufacturing and the potential it offers.

Continuous Manufacturing underpins the improvement of pharmaceutical products in terms of potency, effectiveness and safety by means of accurate process control.

Benefits of Continuous Manufacturing are now evident for the pharmaceutical industry and widely advocated by the regulators through various initiatives, like ICHQ13 guidance and the latest FDA Q13 Continuous Manufacturing Guidance for Industry, which intend to provide scientific and regulatory considerations for the development, implementation, operation and lifecycle management of Continuous Manufacturing.

In fact, continuous mode enhances the adoption of a Quality by Design (QbD) approach. Continuous Manufacturing provides a robust process, increases product quality for higher patient safety, reducing costs and time to market at the same time.

Continuous Manufacturing speeds up product development. A Continuous Manufacturing line can actually be used either for R&D or industrial purposes, since the batch size does not depend anymore on the size of the process vessel, but is simply defined by the time you run the system.

IMA Active has been cultivating its own knowledge and is ready to welcome the demand for innovation, working together with companies and stakeholders to design the future of pharmaceutical manufacturing.

IMA Active proposes Continuous Manufacturing lines for compression, coating and encapsulation of Oral Solid Dosage (OSD) forms as a single partner of integrated solutions based on flexibility and modularity.

IMA'S WAY TO CONTINUOUS MANUFACTURING

IMA Active is now ready for the paradigm shift in pharmaceutical manufacturing and taking the lead in the future of pharmaceutical technologies for OSD forms.

IMA Active's belief in and knowledge of Continuous Manufacturing have grown stronger thanks to intensive R&D work carried out on two fronts.

END-TO-END CONTINUOUS MANUFACTURING

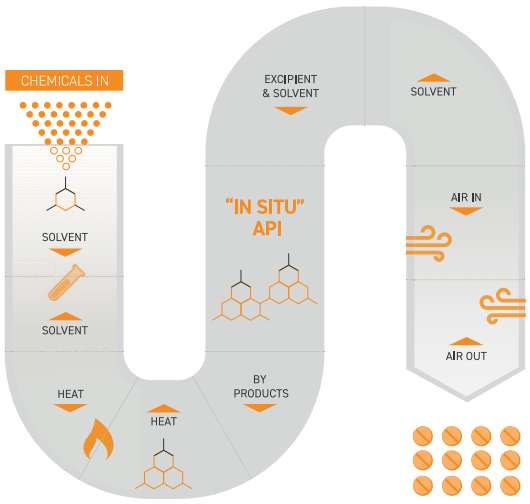
PARTNERSHIP WITH CONTINUUS™ pharmaceuticals

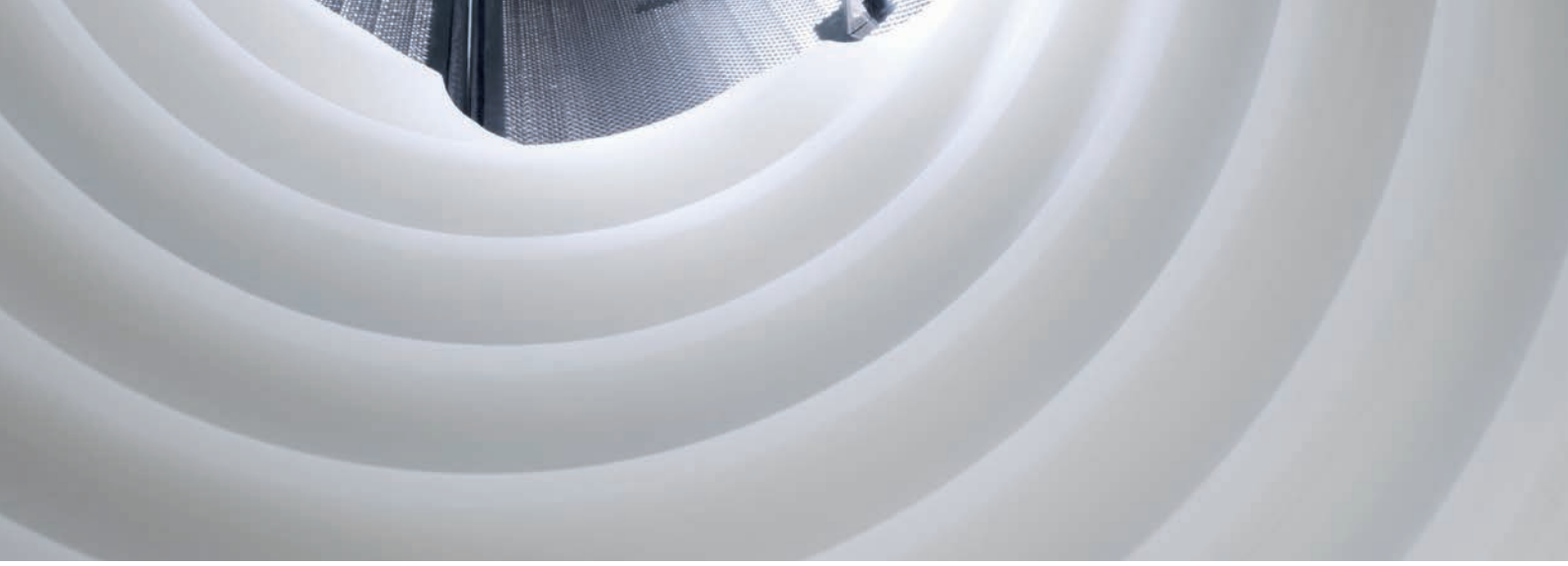
INPUT — API PRECURSOR

OUTPUT — UNIT DOSE

A more disruptive front of IMA Active R&D consists in the partnership with CONTINUUS Pharmaceuticals, a spin out of Novartis-MIT Centre, leveraging a novel production platform called Integrated Continuous Manufacturing (ICM). ICM enables seamless end-to-end Continuous Manufacturing processes that incorporate API formation steps with final drug product formulation.

IMA Active supports ICM in the development of EMC (Extrusion Molding Coating) technology to create the final dosage form.



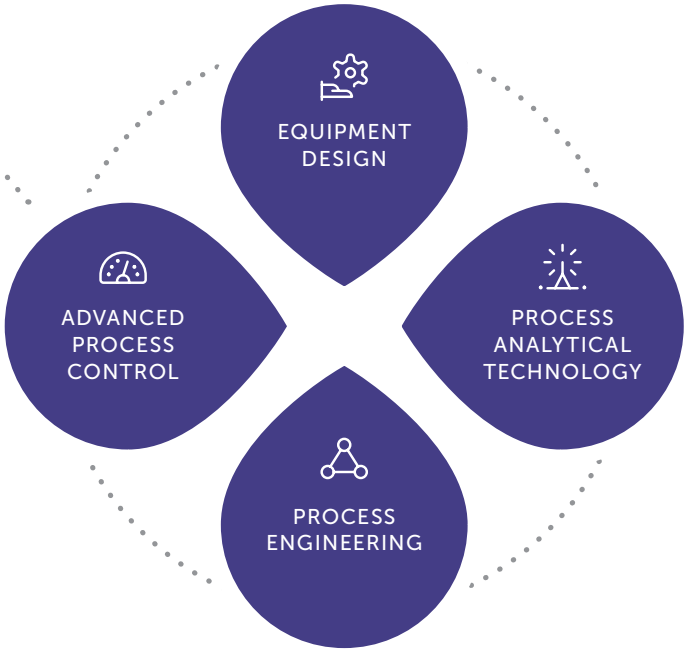


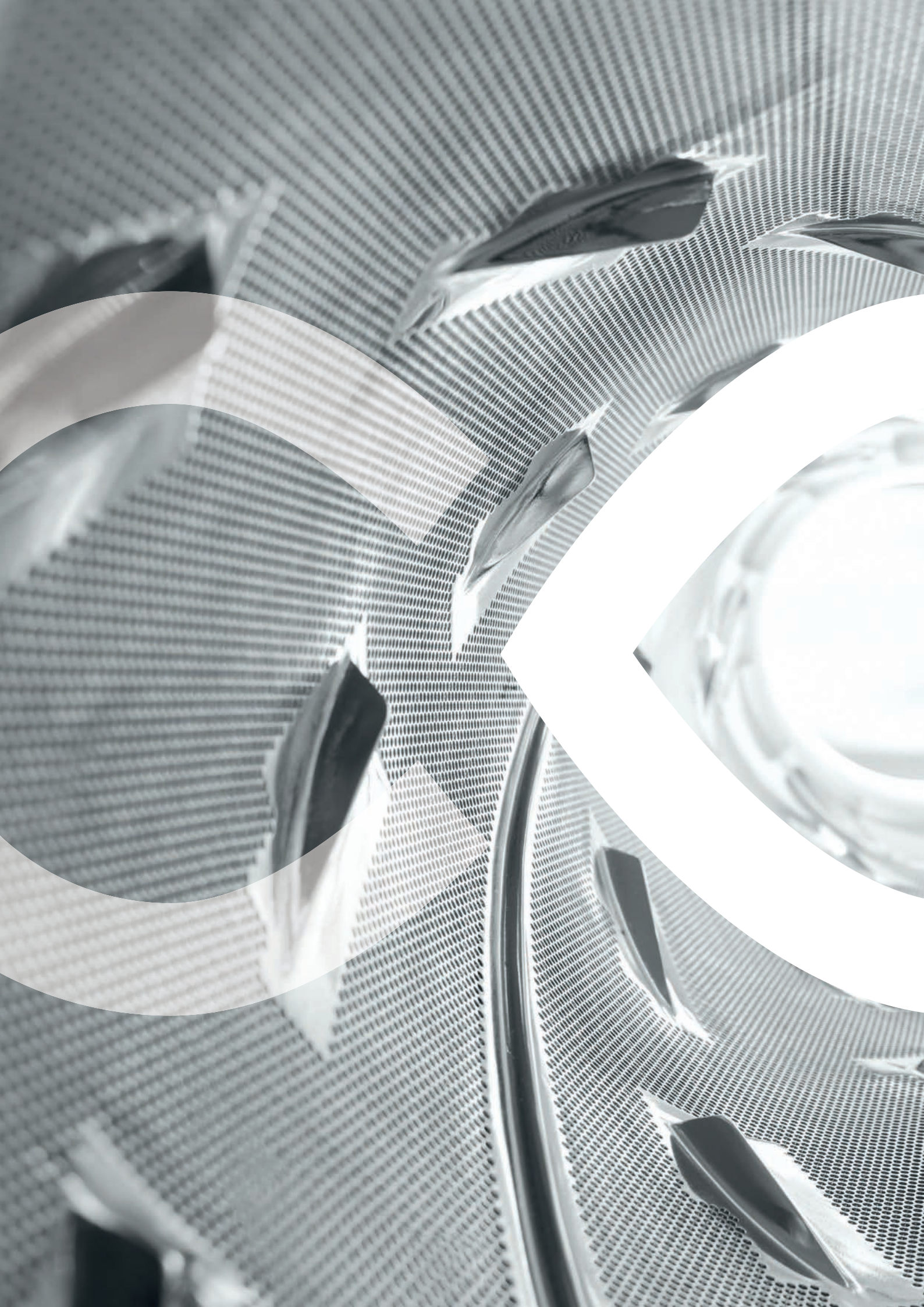
While on the other R&D front IMA Active works on continuous processes by revisiting current technologies, embracing a concept of Continuous Manufacturing more closely related to conventional solid forms.

This initiative aims primarily to introduce continuous equipment into the market that can be integrated with usual technologies, even in an existing plant, in order to improve the production performance.

CONVENTIONAL CONTINUOUS MANUFACTURING

AREAS WHERE IMA ACTIVE CAN PROVIDE A SIGNIFICANT CONTRIBUTION TO DEVELOP MODERN MANUFACTURING





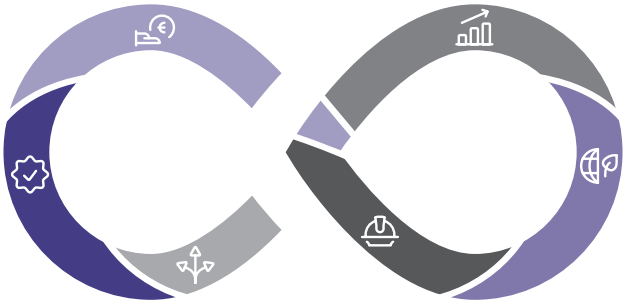
INTO THE FLOW

Based on more than 50 years' process experience, IMA Active would like to involve you and rapidly illustrate the benefits of continuous processing.

IMA Active contributes to making Continuous Manufacturing available for all and not just for a small elite of pharmaceutical manufacturers.

CONTINUOUS FLOW OF BENEFITS

Though Continuous Manufacturing is still considered a challenge, it is common knowledge that it brings significant advantages like cost and risk reduction at all stages, either during the engineering phase or in daily production with the opportunity of higher flexibility.



CONTINUOUS MANUFACTURING IN THE PHARMACEUTICAL INDUSTRY UNDOUBTEDLY HAS GREAT POTENTIAL

QUALITY

- QbD approach bringing reduced time for quality control and test release.
- Reduced risk of human errors due to a high level of automation.

FLEXIBILITY

- Batch size and production volumes are defined by runtime. No more constraints due to equipment size.
- Flexibility in process flow thanks to modularity of the CM operations.
- CM unit operations are compact, designed with standard connections and minimum utilities, conceived for easy and quick installation to replicate in any manufacturing site worldwide with a short startup time.

SUSTAINABILITY

- Reduced plant footprint which means smaller equipment, no more need of work-in-process inventory, less personnel, with consequent space and energy savings.
- Lower environmental impact through reduced utility consumption.
- Reduced process surface to clean: less water consumption.
- Less risk of drug shortage thanks to reduced time to market.

COSTS

- Important contribution for reducing costs includes smaller equipment and fewer manufacturing steps, with consequent saving for installation, validation and maintenance. In addition, rapid development, improved yields, less personnel achieve overall estimated cost reduction range from 30% to 50%, with impact on drugs affordability as well.

SAFETY

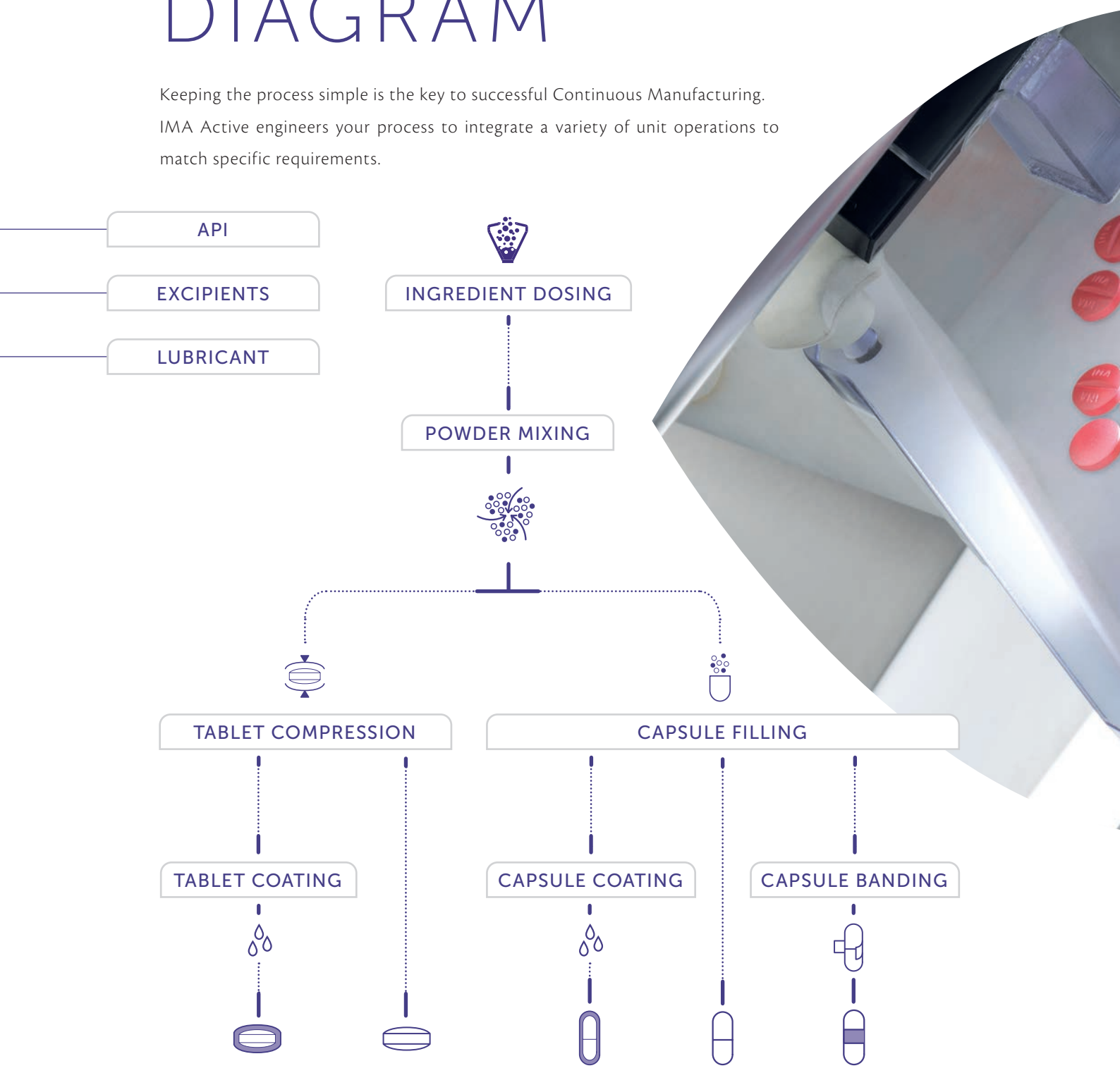
- Patient safety is ensured by adoption of QbD and PAT (Process Analytical Technologies). Minimum risk to fall OOS (Out-of-Specifications).
- Operator safety provided by lower risk of exposure means reduction of PPE.
- Operators are better protected since product handling, process space and air displacement are significantly reduced.

EFFICIENCY

- Shorter time to market due to quicker product and process development, minimisation of process scale-up.
- Significant increase in productivity and improvement of OEE generated by:
  - Faster production time, also by minimising product handling.
  - Reduction of waste and losses.
  - Quicker changeover due to minimum downtime.

CONTINUOUS PROCESS FLOW DIAGRAM

Keeping the process simple is the key to successful Continuous Manufacturing. IMA Active engineers your process to integrate a variety of unit operations to match specific requirements.



To gain all the benefits of switching from batch to Continuous Manufacturing, it is first recommended to reduce the overall complexity of the process by decreasing the number of steps, consequently lowering the number of process variables. Therefore, Continuous Direct Compression (CDC) or Encapsulation (CDE) are the preferred technologies from where to start the transition from batch to Continuous Manufacturing.

POWDER DOSING

Powder dosing represents the base for continuous production of OSD forms and becomes crucial for CM. Proper dosing of each ingredient is ensured by using Loss-In-Weight (LIW) feeders that are equipped with load cells able to accurately feed the mixer downstream. The feeding unit is customised according to the number of ingredients, range of dosage and type of refilling system.

POWDER MIXING

The mixer is designed to suit the feeding unit, dimensioned according to required throughput, with mixing blades adequate for the powder's properties.

TABLET COMPRESSION

Rotary tablet press is suitable for continuous technology by definition. When integrated in a CM line it is equipped with the proper controls to interact with the feeding blending unit upstream. All IMA Active tablet presses are designed with particular attention to providing maximum performance for direct compression.

COATING

CROMA coater has been specifically designed to provide a truly continuous coating technology. It can work downstream from a tablet press or a capsule filler. ACCELA CTC continuous coaters by Thomas Processing complete the IMA Active range of continuous coating equipment, particularly suited to very high throughputs or large batches.

CAPSULE FILLING

IMA Active capsule fillers with all their prerogatives in dosing and weight controls are particularly suitable for being prime unit operations of a CM line.

CAPSULE BANDING

A capsule banding machine for tamper-evident sealing can be considered among the possibilities to complete a CM line.

INTEGRATED CONTROL SYSTEM

MAESTRO, IMA Active's integrated control system, ensures that all the above mentioned unit operations work as a single system.

CONTINUOUS DIRECT COMPRESSION

CDC is a very lean, efficient and flexible tablet-manufacturing technology that, in combination with PAT, allows easy adoption of a QbD approach. FDA has recently graduated CDC technology to go through the standard quality assessment process. CDC provides excellent operation performance; the system is designed to achieve a state of control very quickly and avoid any waste during startup and shutdown phases.

A CDC line has a lean configuration which promotes smooth product flow, consisting of unit operations to configure:

- **A SET OF FEEDERS**
  (up to 6 units)
- **HORIZONTAL MIXER**
- **TABLET PRESS**
- **INTEGRATED CONTROL SYSTEM**

OPTIONS

The CDC line can be equipped for advanced processing with the following options:

- **MATERIAL HANDLING FOR FEEDERS REFILLING**
  (by gravity or pneumatic transfer)
- **MATERIAL IDENTIFICATION**
  (bar code reader, NIR probe, etc.)
- **FULL INTEGRATION OF PAT SENSORS**
- **PROCESS MODELLING AND OPTIMISATION**
- **KIT OF SPARE PARTS**
  (to reduce downtime while washing off line)
- **WET-IN-PLACE**
- **HIGH CONTAINMENT**
  (split valves, isolator glove ports, etc.)
- **INTEGRATION OF ROLLER COMPACTOR**
  (for dry granulation)
- **INTEGRATION OF CONICAL MILL**

RECOMMENDED AVERAGE THROUGHPUT FOR PHARMACEUTICAL MANUFACTURING IS USUALLY 20-100 KG/H. HIGHER THROUGHPUT IS ALSO AVAILABLE CONSIDERING DOUBLE-SIDED TABLET PRESS, WHILE FOR VERY SMALL THOUGHPUT BELOW 20 KG/H A MINI-BATCH FEEDING BLENDING UNIT CAN BE COMBINED WITH A SMALL ROTARY TABLET PRESS. MINI-BATCH CONCEPT CONSISTS OF A RAPID AUTOMATIC SEQUENCE OF SMALL BATCHES.

Continuous coating is a further manufacturing step that can be considered either straight inline or as a separate and subsequent step with regard to CDC. IMA Active makes use of its strong background in coating proposing two different novel continuous technologies.

CDC WITH CONTINUOUS COATING

TWO TECHNOLOGIES, FOR ANY NEED

CROMA continuous coater is IMA Active's novel technology for a fast and truly continuous process. Designed to be modular to manage a range of tablets throughput and a range of coating weight gain. A single CROMA module works in ranges of 20-100 kg/h and average 2-4% weight gain, depending on tablets and film types. CROMA versatility allows to manage with one equipment size product development, clinical trials and manufacturing, with no need of scale-up. CROMA working principle is based on a traditional coating system.

Uncoated tablets transit a perforated drum in a continuous flow, where they are mixed subjected to a flow of hot air and coated with liquid polymer using spray guns.

Featuring the continuous coating technology pioneered by Thomas Processing, ACCELA CTC is designed to manage high production throughputs between 100 and 1,200 kg/h, processing large tablet batches in continuous mode.

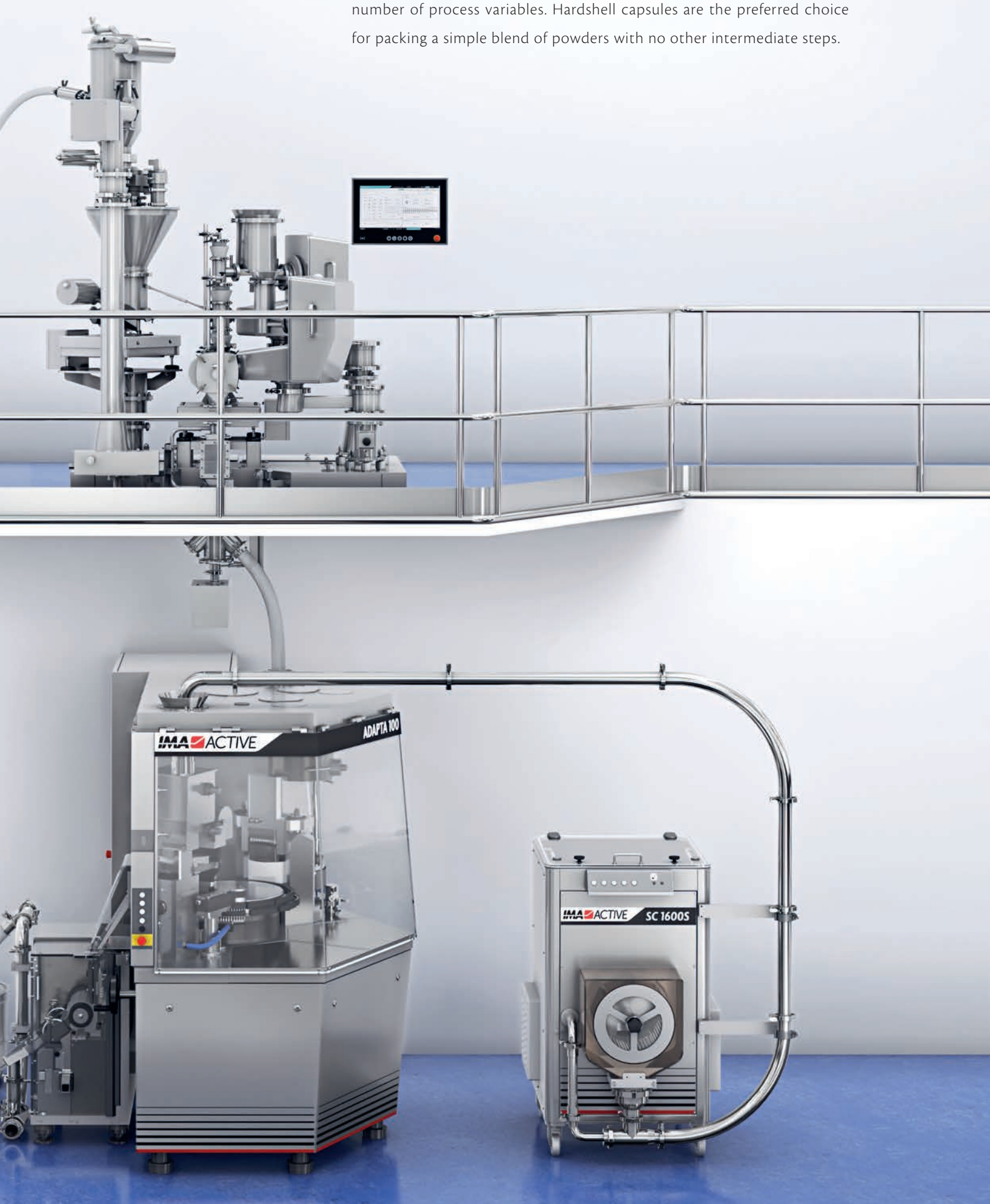
The equipment's advanced design eliminates material waste from the process and avoids reprocessing during startup and shutdown.

ACCELA CTC, unique in the market, integrates a standard curing chamber and optional wax addition system, streamlining the coating process while minimising overall equipment footprint.

ACCELA CTC can be equipped with automatic Wash-In-Place (WIP) system.

CONTINUOUS DIRECT ENCAPSULATION

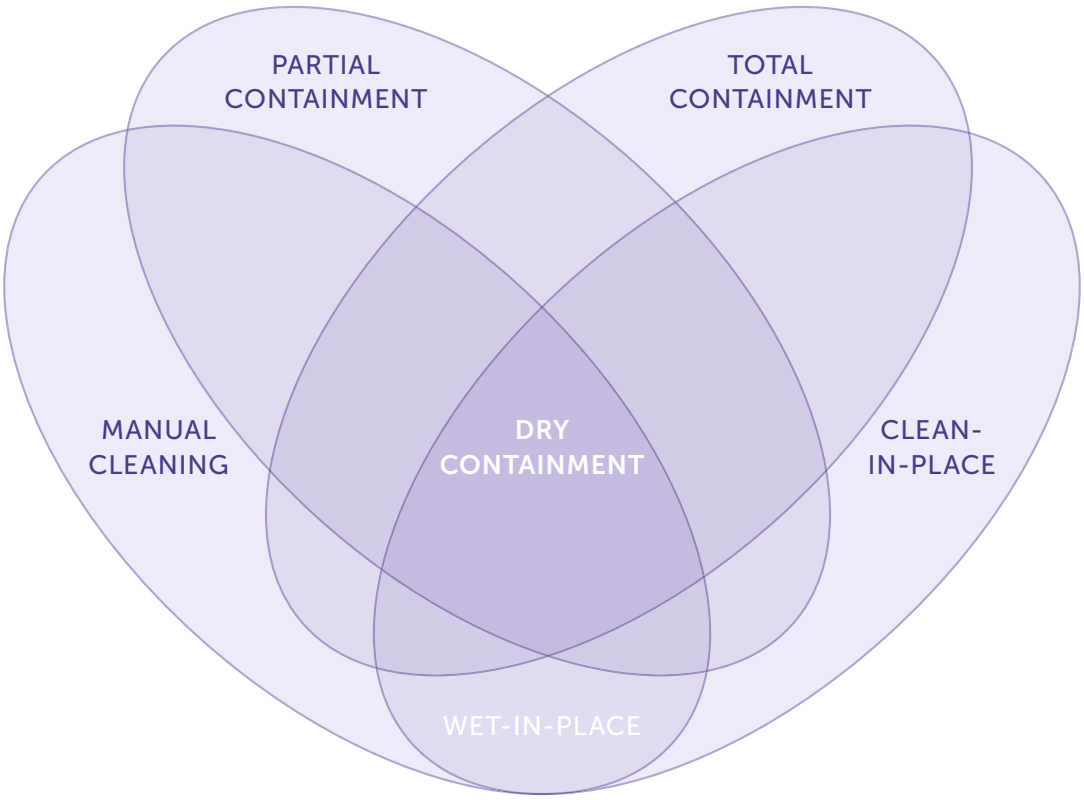
All the benefits of Continuous Manufacturing are gained by reducing the overall complexity of the product lifecycle and by decreasing the number of process variables. Hardshell capsules are the preferred choice for packing a simple blend of powders with no other intermediate steps.



CONTINUOUS MANUFACTURING IN OPERATION

The increasing complexity of drugs, as well as the emergence of new solid dosage forms, has led to the need for advanced manufacturing technologies and flexible production throughput. Customized equipment and suites, flexible manufacturing lines and approaches are critical to reaching the pharmaceutical market timely and successfully. IMA Active can be the overall strategic partner for pharmaceutical companies, agreeing and sharing the requirements in order to achieve the most appropriate configuration of a Continuous Manufacturing line, combining process and equipment design.

THANKS TO THE LARGE PORTFOLIO OF MATERIAL HANDLING EQUIPMENT, IMA ACTIVE CAN OFFER A WIDE VARIETY OF SOLUTIONS FOR PRODUCT TRANSFER FROM ONE UNIT OPERATION TO THE OTHER.
OF COURSE, THIS IS TO BE DESIGNED IN ACCORDANCE WITH AVAILABLE SPACE, OPTIMISING INSTALLATION AND UTILITIES, WHILE ENSURING SUSTAINABILITY.
IMA ACTIVE IS ABLE TO HANDLE DIFFERENT APPROACHES REGARDING CONTAINMENT, SAFETY AND CLEANING.



PROCESS CONTROL

Process control can be enhanced with full integration of PAT tools and use of mathematical models for measurement or prediction of Critical Process Parameters (CPP) that determine Critical Quality Attributes (CQA).

Process data collection from each unit and their proper management provide full understanding and favour continuous process improvement.

In this way, the critical process parameters can be managed until diversion criteria are defined, so that only out-of-specification dosage forms are discarded and the rest of the lot is preserved.

To facilitate this task, it is recommended to rely on state-of-the-art sensors able to measure quality attributes (e.g. moisture content, API content uniformity, blend uniformity, coating uniformity, etc.). These are the so-called PAT sensors.

EXAMPLES OF PAT SENSORS

- **WEIGHING UNIT**
  In-line weight control for capsules or tablets
- **IRIDE IMAGING DEVICE**
  At coater exit chute to check colour uniformity

● NIR

On tablet press feed frame to check content uniformity

● NIR

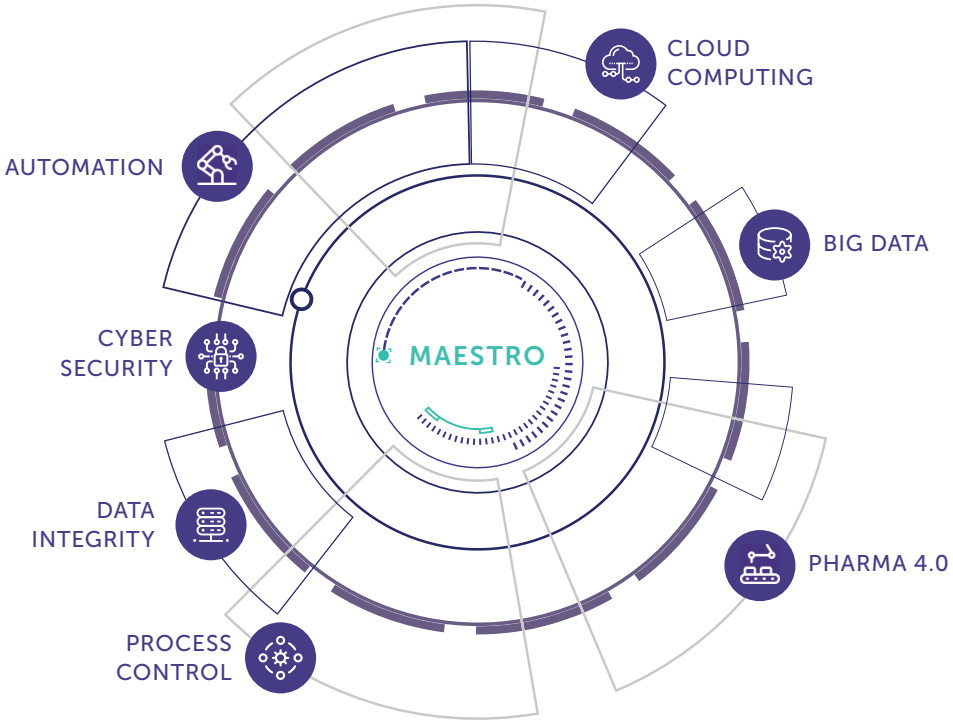
At coater exit chute to check coating quality

MAESTRO INTEGRATED CONTROL SYSTEM

MAESTRO has been developed with a clear understanding of how to support FDA's initiative for QbD and with the primary objective of simplifying and expediting Continuous Manufacturing in the pharmaceutical industry.

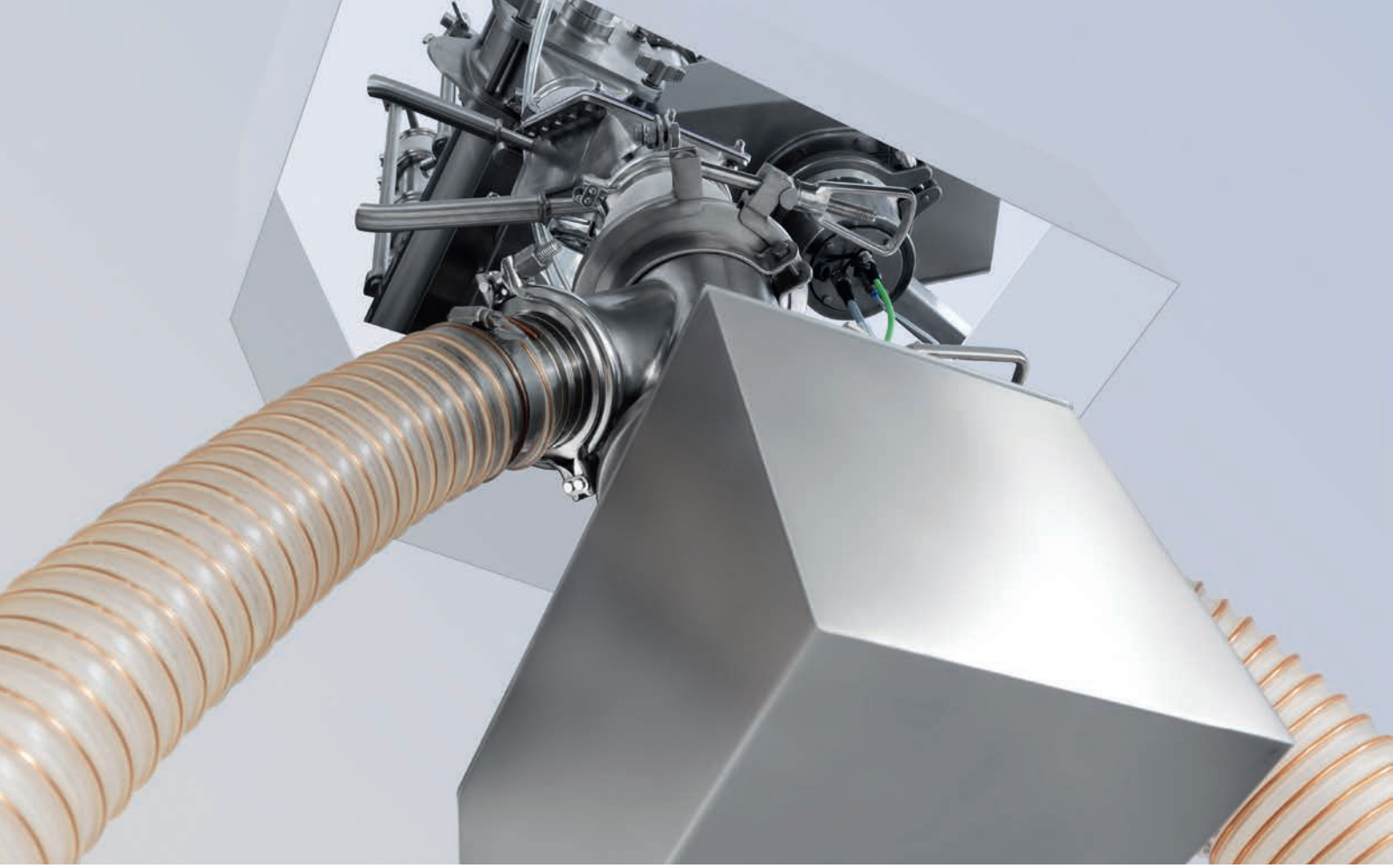
Just as batch manufacturing does, Continuous Manufacturing also requires a comprehensive and holistic control strategy throughout the product lifecycle to ensure, in a consistent and reproducible manner, the intended product quality at the time of release and throughout the product's shelf life.

A RELIABLE AND VERSATILE ORCHESTRATION SYSTEM IS THE KEY TO MAINTAINING QUALITY AND MAXIMISING PRODUCTION EFFICIENCY. DATA INTEGRITY IS A CRUCIAL AREA WHERE MAESTRO FACILITATES QUALITY CONTROL BY COLLECTING, AGGREGATING AND PRESENTING VARIOUS DATA AND INFORMATION.



MAESTRO

- Has a modular design for easy integration of different unit operations.
- Is the modular orchestration layer that manages the entire CM line as a single system, regardless of the number of units involved.
- Integrates the operations between the units with a robust communication protocol.
- Empowers the real value of using one single system with an interface that dynamically tailors its content on each user's role.
- Promotes simplicity over complexity, allowing users to perform tasks safely, effectively and efficiently.



MAESTRO guides operators so that they focus their attention on strategic parameters, avoiding unwanted information. It also provides a clear guide to all the additional activities required to prepare a production run, avoiding errors and waste of time.

TYPICAL SEQUENCE OF BASIC OPERATIONS FOR A CDC LINE

1. OPEN A LOT FOR THE WHOLE CDC LINE WITH A SINGLE COMPREHENSIVE RECIPE
2. CARRY OUT LINE PREPARATION
3. ACTIVATE ORDINARY PRODUCTION MODE
4. THE SYSTEM AUTOMATICALLY MANAGES THE STARTUP PHASE FOR EACH SINGLE UNIT UNTIL STEADY STATE IS REACHED
5. PAT ON TABLET PRESS MONITORS AND CHECKS TABLET QUALITY BY DIVERTING GOOD AND WASTE, IF ANY
6. BEFORE CLOSING THE LOT, THE SYSTEM PERFORMS THE SHUTDOWN PHASE ON EACH UNIT
7. THE PRODUCTION REPORT IS A SINGLE AND COMPLETE DOCUMENT FOR THE WHOLE CDC LINE

MAESTRO

BASIC ORCHESTRATION FEATURES

MANAGEMENT OF RECIPES
one single recipe for the entire production

GMP DATA
alarms, events and audit trials

USER AND DATA SECURITY
user authentication, customisable access rights and profiles

DATA MANAGEMENT
process reports

MAESTRO PLATFORM ADDRESSES TODAY'S DEMANDS FOR COMPLETE AND RELIABLE PROCESS CONTROL, USABILITY, FLEXIBILITY AND CONNECTIVITY.

ADVANCED FEATURES

MULTIPLE HMIs FOR MAXIMUM ERGONOMICS

MATERIAL GENEALOGY

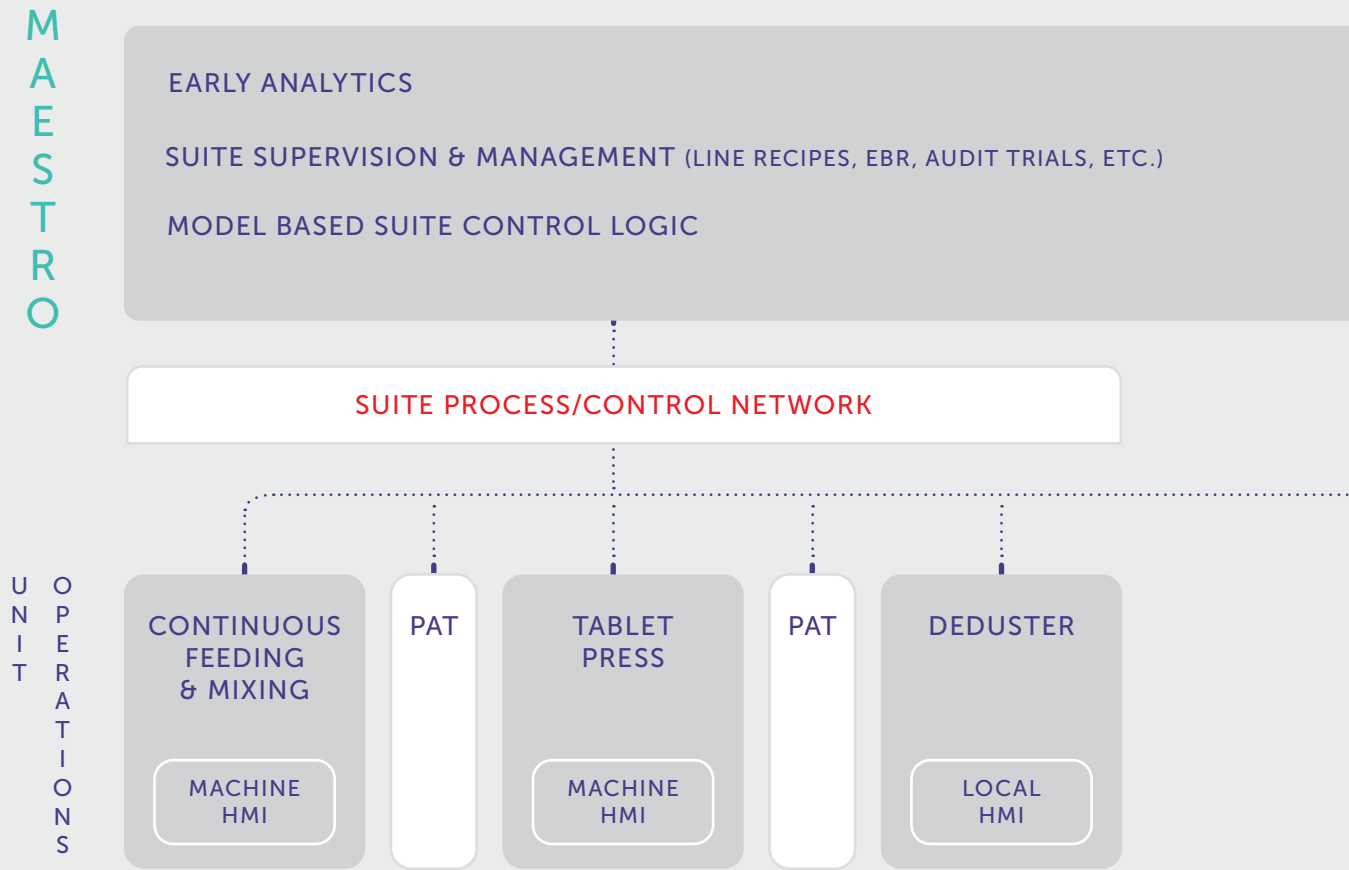
DIRECT INTEGRATION OF PAT INSTRUMENTS

MATERIAL TRACKING

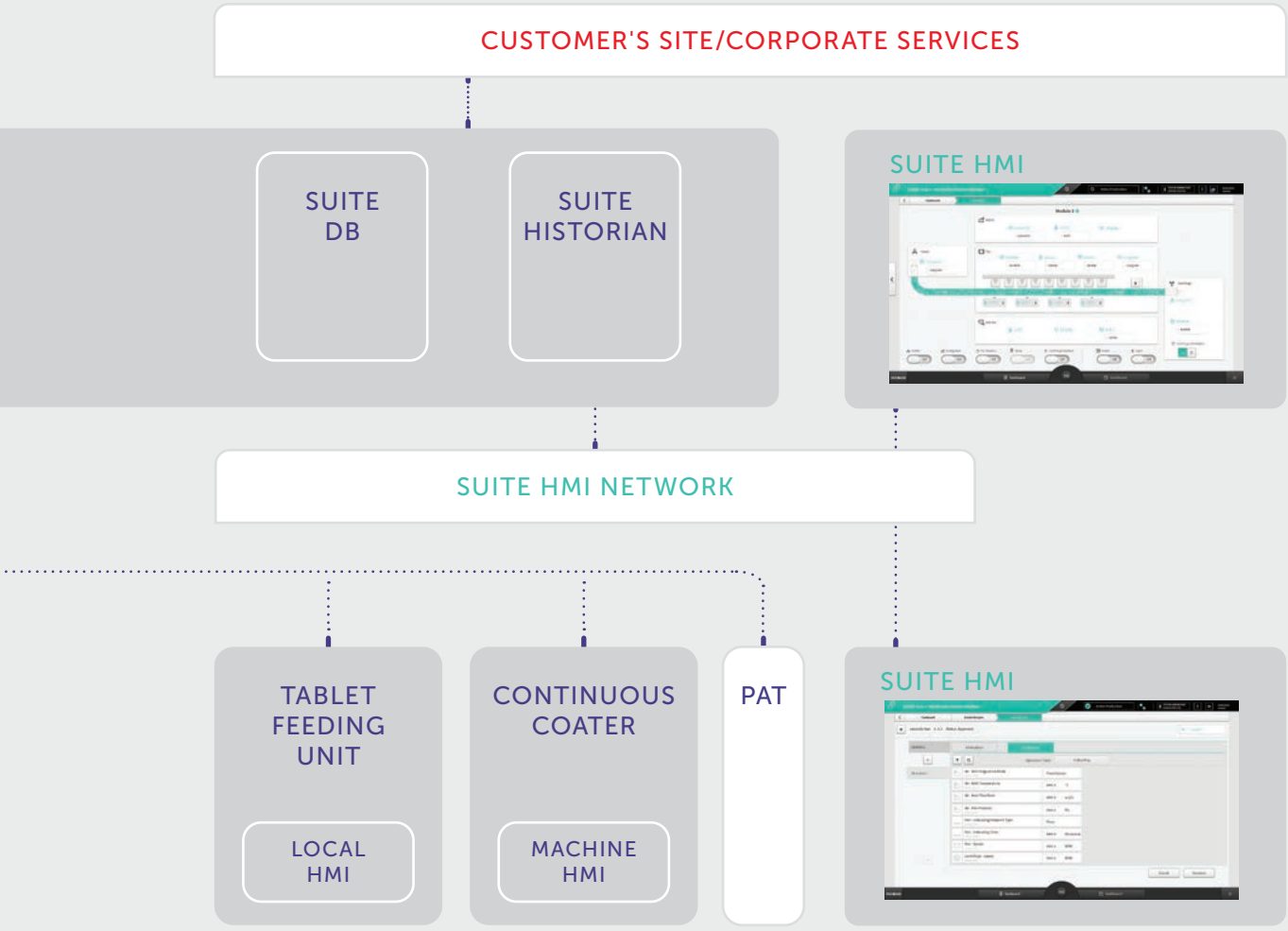
ADVANCED DATA COLLECTION AND AGGREGATION

MAESTRO ARCHITECTURE

MAESTRO fits seamlessly into a modern connected factory, matching the evolution of the digitalization process, using widely adopted communication standards such as OPC UA and aggregating data in the PackML scheme to be easily understood. With the IMA Digital initiative, the connection strategy meets the highest security requirements for an industrial communication network with proven and documented protection against cyberattacks.



EACH UNIT OF A CM LINE MAINTAINS ITS OWN CONTROL SYSTEM. STILL, PRODUCTION OPERATIONS AND THEIR RELATED SET-UP PHASES ARE ENTIRELY MANAGED WITHIN THE MAESTRO ENVIRONMENT. THE CLEVER INTEGRATION STRATEGY OF THE CONTROL SYSTEM OF EACH SINGLE UNIT AND THE EFFECTIVE PROCESS CONTROL BETWEEN THEM ENHANCE THE AUTOMATION OF EVERY SINGLE UNIT OPERATION.



MAESTRO COMPLETES IMA ACTIVE PROJECT TO HARMONISE HMI AND SCADA SYSTEM ENHANCING USER EXPERIENCE IN A MODERN DIGITAL FACTORY. IN THIS PROJECT, IMA ACTIVE HAS APPLIED SKILLS FOR EQUIPMENT DESIGN AND MACHINE INTEGRATION IN COMBINATION WITH PROCESS EXPERTISE IN A REAL QbD APPROACH.

MAX HUMAN MACHINE INTERFACE

COMMUNICATION AREA

Informs and connects the people involved in the production

MULTI-USER VIEW

Different content for each user profile

USER GUIDE AREA

Wizards to minimize errors and timing

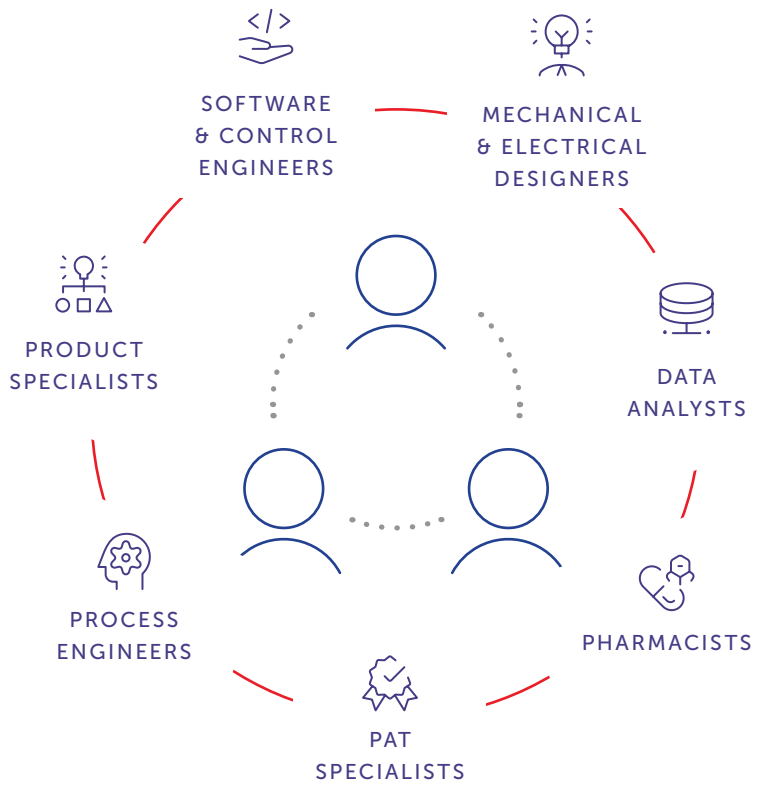
CONFIGURABLE AREA

Collection, monitoring and data display

MULTIDISCIPLINARITY AND COOPERATION

IMA Active supports innovation in manufacturing by bringing together all the necessary competences: Process Engineering, Equipment Design, Process Control and Process Analytical Technology.
Evolving market needs have been evaluated resulting in a multidisciplinary approach that supports any kind of pharmaceutical company, facilitating the adoption of Continuous Manufacturing.

TO BETTER UNDERSTAND END-USERS AND MATCH THEIR NEEDS, IMA ACTIVE HAS BROUGHT IN ITS R&D TEAM PEOPLE WITH DIFFERENT SKILLS AND A HIGH LEVEL OF COMPETENCE. ONLY A MULTIDISCIPLINARY APPROACH CAN GENERATE EFFECTIVE TECHNOLOGIES FOR THE FUTURE OF PHARMACEUTICAL MANUFACTURING.



IMA ACTIVE HAS BEEN SHARING THE SAME VISION WITH SOME STRATEGIC PARTNERS TO PROVIDE A GLOBAL CONTINUOUS MANUFACTURING PROPOSAL. THE RESULT IS A NETWORK OF PARTNERS DELIVERING SERVICES TO THE PHARMACEUTICAL SEGMENT. THIS LEADS ULTIMATELY TO A PRODUCTIVE COLLABORATION IN WHICH ALL THE STAKEHOLDERS ENGAGE WITH THEIR RESPECTIVE ENERGIES AND COMPETENCES.

IMA ACTIVE COMPETENCE CENTER

The change from batch to continuous involving innovative technologies also requires a testing phase. Process experts at IMA Active Competence Center are available to support individual cases.

TEST YOUR SWITCH TO CM AT THE IMA ACTIVE COMPETENCE CENTER

FEASIBILITY STUDY FOR THE WHOLE CM

EVALUATION OF INDIVIDUAL UNIT OPERATION
(Loss-In-Weight feeders, mixer, tablet press, coater)

PATH FOR PROCESS UNDERSTANDING

FEASIBILITY OF PAT APPLICATION


PREXIMA 300
IMA ACTIVE
CROMA

IMA ACTIVE

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