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How Development and Manufacturing will need to be structured

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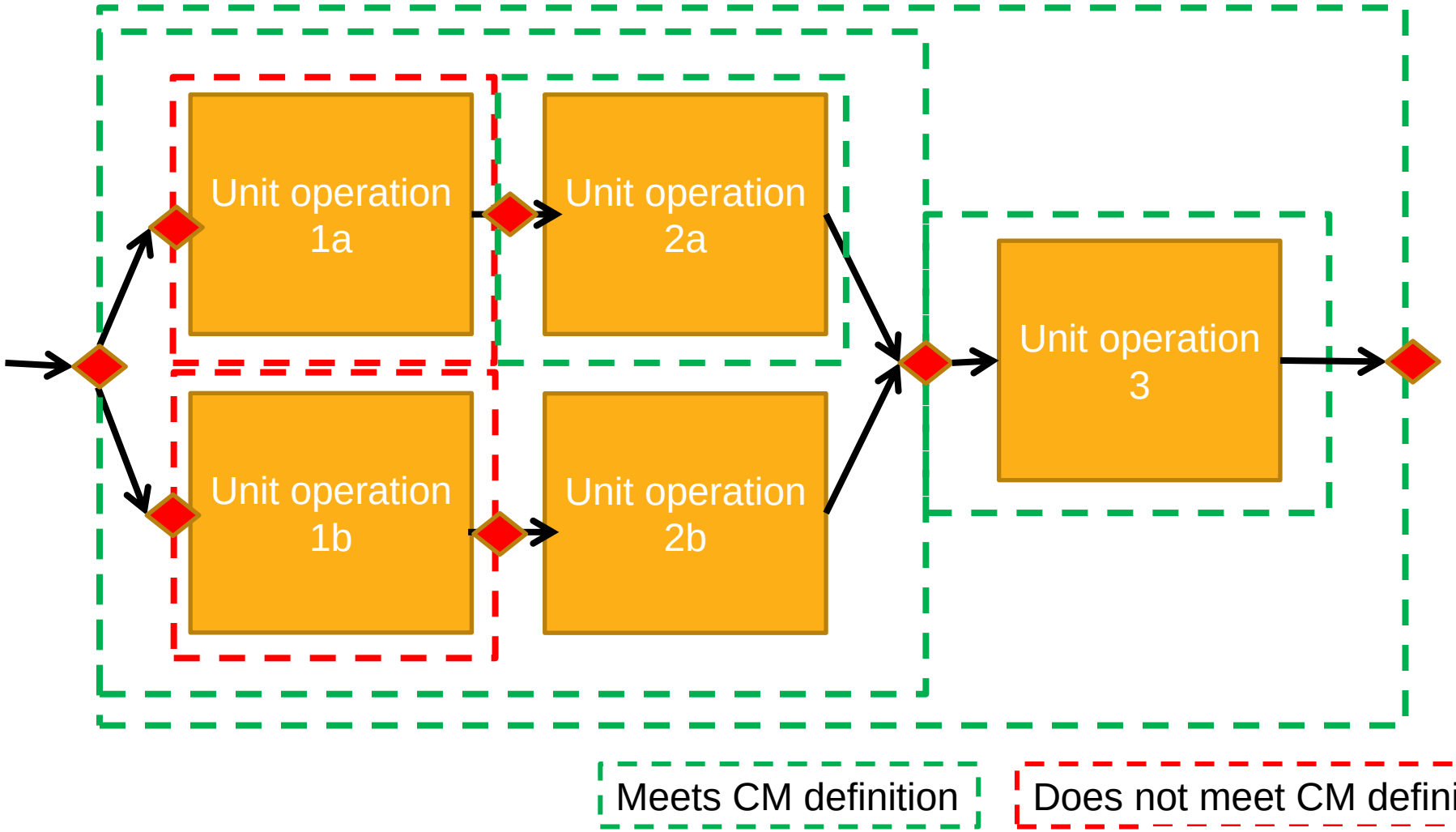
CM Definitions or Key attributes

- Flow= simultaneous inlet and outlet of materials
- Systems approach to design
- Integration
- Automated control
- Classification is a matter of scale

CM Definition is a matter of scale



CM implementation scenarios

- Implementation scenarios
  - Opportunistic=stepwise identification of promising unit ops based on performance factors like yield, purity, throughput etc. in a bin to bin setting
    - Control anchor points at bins
  - sequences= sets of short sequences are grouped together in a bin-to-bin setting
    - Control anchor points at bins before and after sequence
  - Complete chemical or pharmaceutical chain
    - Control anchor points “plant-wide” within each stream
    - Allows consistent volume streams within each discipline
  - E2E across Drug Substance and Drug Product
    - Requires plant-wide control
    - Offers most benefits, but dosing strengths stress matching volume streams

CM implementation in Development

Unique differences to traditional batch approach

- How to pick the best suited candidates early in development?
- Dynamic characterization of transformations is essential
- As the desired degree of integration grows, more risk mitigation is needed to cover the desired process chain

⇨ CM=Frontloading Development activities

- Implementation in Discovery may help to identify structures that lend themselves to CM synthesis - But it is recognized that this will always be secondary to biological activity and bioavailability
- Materials can be made available in larger quantities easier, but larger quantities are needed earlier as well
- CM needs different experimental procedures, more kinetic information earlier, but gain in late phase
- Fewer scale up steps = development in large scale?

⇨ CM=payback in late stage

Structural consequences of CM in Development

- The ability to scout out the portfolio early will require a dedicated CM scouting group with CM specific objectives
- Early phase CM-specific mindset to think in process trains instead of steps requires more complex thinking, initially this time=headcount
- Early phase KPIs will suffer compared to batch
- More kinetic information needed early in the development process → skillset shift towards integrated multidisciplinary groups
- Late phase allows much more complex QbD scenarios easily requiring less material
- More structural thinking and Quality driven mindset = higher demand in highly educated personnel and fewer but higher skilled operators
- Technical skills will see more demand (automation, process engineering, simulation skills)

CM implementation in Technical Operations

- Common features of CM in Technical Operations/Production
  - 24/7 operational mode is key for all operations including 2nd level support functions
  - reliability engineering is key to guarantee uninterrupted operation with regard to equipment and process reliability, stability of media and gaskets, redundancy and hot-plug replacements of components
  - State monitoring is necessary and typically not yet implemented in Pharma
  - Wide adaptation of production rates in late steps of a chain is inevitable and challenging in a long chain, having side effects on OAU/OEE
  - Reliable supply lines for raw materials on time needed or large buffer stocks

CM consequences for Technical Operations

- Operation staff for all functions need to accommodate 24/7, including tech support
- Manufacturing science groups need to accommodate new and much more complex validation and PAT scenarios
- PAT (analytical science and chemometrics) and control engineering will carry more weight
- Quality functions will need less operational QC and more QA systematic functions
- Regulatory oversight will have to deal with systems more than with data driven oversight → shift of focus
- Total E2E integration will unify ChemOps and PharmOps to a CM-Ops, as no handover of responsibility is possible for an end-to-end process

CM implementation in Outsourced operations

- Development needs to be conducted at Originator and then outsourced as packages to separate specialist companies
- Managing a network of suppliers to form a harmonized chain is key
- Total oversight remains solely with originator
- Originator needs to drive all science aspects, but not operational aspects
- Only feasible for bin-to-bin, not for E2E...
  then everything is connected

CM implementation summary

- Every big Pharma organisation can handle opportunistic implementation scenarios with minimal changes in structure, if the skills of the workforce is reflecting needs and build experience and confidence
- The larger the scope of building chains of CM processes, the more structural refinements have to support this effort
- Total integration removes current separation of Chemical and Pharmaceutical operation, organisationally and financially
- Entire business models and centralized vs. decentralized setups can shift following a complete CM adoption

Discussion

2 questions per table, please

Is that the current state of Pharmaceutical sciences?

"Current development and in-line technical support functions completely lack the skills, the organization and the mental framework for CM to be successful in our industry; they hold us back from the next logical step in our evolution."