

Going against the flow

An AstraZeneca view of continuous manufacturing

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CMAC

Continuous Manufacturing
and Crystallisation

Outline

The Challenge

The Value Proposition

AZ Activities

The role of CMAC



Context

A challenge unique to the Pharma Industry?

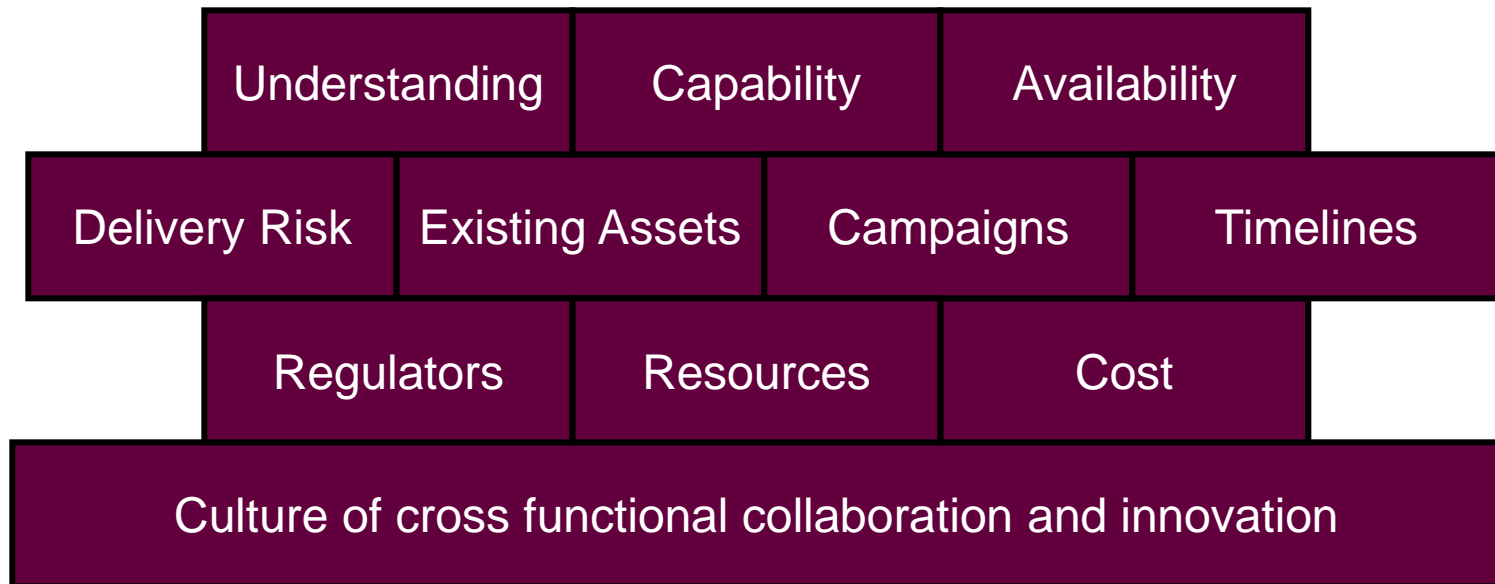
- Attrition
 - Only a small percentage of what we work on in R&D will become a commercial product.
- Regulation
 - The industry is highly regulated, risk averse and conservative.
- The Product
 - A safe, efficacious, differentiated (and increasingly reimbursable) clinical outcome, not the medicine itself.
- This challenges the adoption of potentially costly, poorly understood new manufacturing methodologies and technologies.



More than just a technical challenge ...

“A strategy of process intensification requires a step change in the philosophy of plant and process design. If effectively implemented it will lead to major improvements in environmental acceptability, energy efficiency, intrinsic safety and capital cost. A major cultural change is required on behalf of chemists, engineers and managers and it is this, rather than technical difficulty which represents the main obstacle to progress”.

Prof. C Ramshaw



The Value Proposition

Enhancing reputation

“Pharmaceutical quality management is lacking and we are not anywhere near where we need to be ... the whole mantra of the quality revolution is to meet customers’ needs, and that drives everything. Manufacturing variation should be well understood and controlled.”

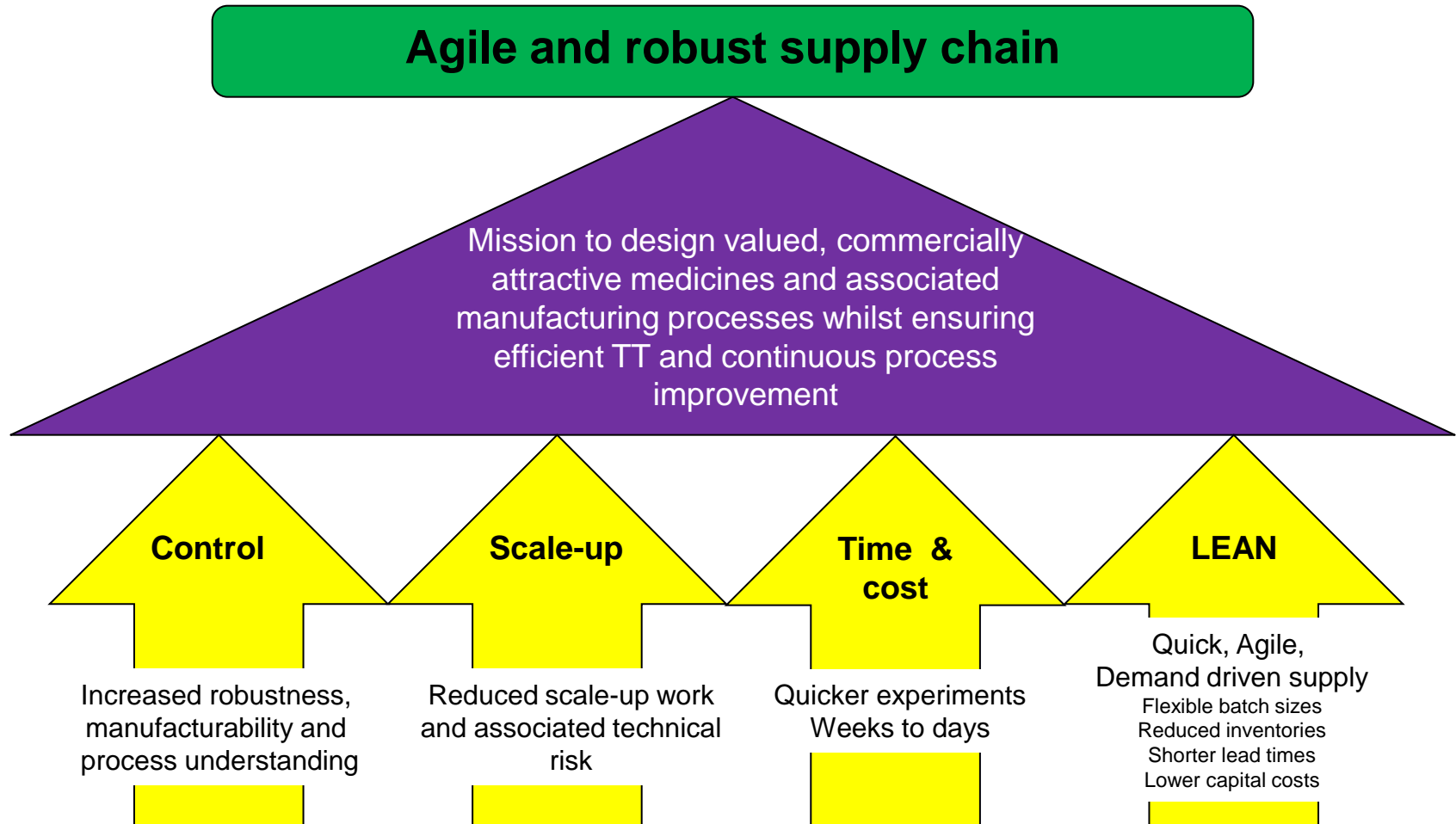
Janet Woodcock, FDA

- Increased flexibility
 - Moving processes between sites
- Improved process robustness
 - Value of producing the same product every time.
 - Hidden cost of NRFT manufacturing (e.g. Increased QC)
 - Value of working capital
- Environmental sustainability
- Cost of goods
 - Increased selectivity, controlled particles, lower cost drug product manufacture
- New IP
- Better than generic / low cost suppliers



The Value Proposition

Better Supply Chains



UNDERPINNED BY ADVANCES IN MANUFACTURING SCIENCE INCLUDING FLEXIBLE AND CONTINUOUS PROCESSES



The Value Proposition

Exploding the myths

- Continuous is not ...
 - Only suitable for large volumes
 - 10kg/day = 3tpa, up to 20 tpa
 - Uses HPLC pumps, it is a highly controlled laboratory suitable for commercial manufacture of niche products
 - It may in fact be more applicable for smaller volumes!
 - Unique and product specific
 - A regulatory challenge, but we could influence this further
 - Several examples (Pfizer, GSK, Novartis, Genzyme, DSM)
 - End to end
 - Iconic project, but not essential for value generation
 - The only option
 - Various estimates, perhaps up to 15%
 - However, the more we overcome the challenges ...



Continuous Manufacturing in AZ

Linking API and Drug Product

Measurement, analysis and control

API Process Development and Manufacture

Particle Engineering

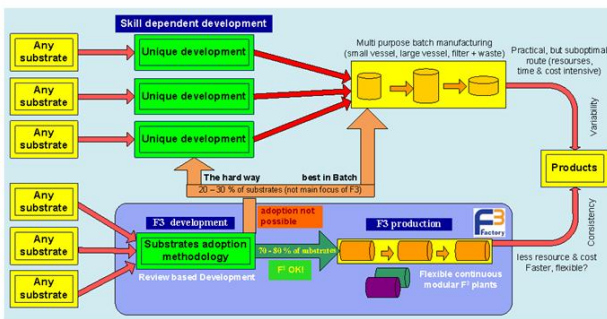
Drug Product Process Development and Manufacture

Identify, understand, implement and exploit continuous processing where it adds tangible benefits

Design and deliver the right API particles

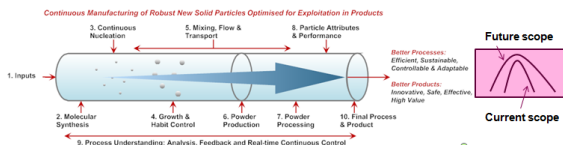
Replace wet granulation with continuous dry granulation

Transformation Sub project



EPSRC Innovative Manufacturing Centre

Vision: to accelerate the adoption of continuous manufacturing processes, systems and plants for the production of high-value chemical products



Initial Focus of EPSRC Centre Programme

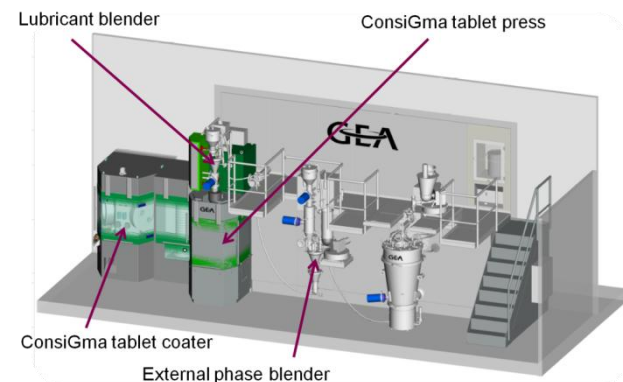


Continuous Manufacturing and Crystallisation



35 researchers and growing.

DTC = 15 PhDs / year from Q4 2013



API Process Development and Manufacture

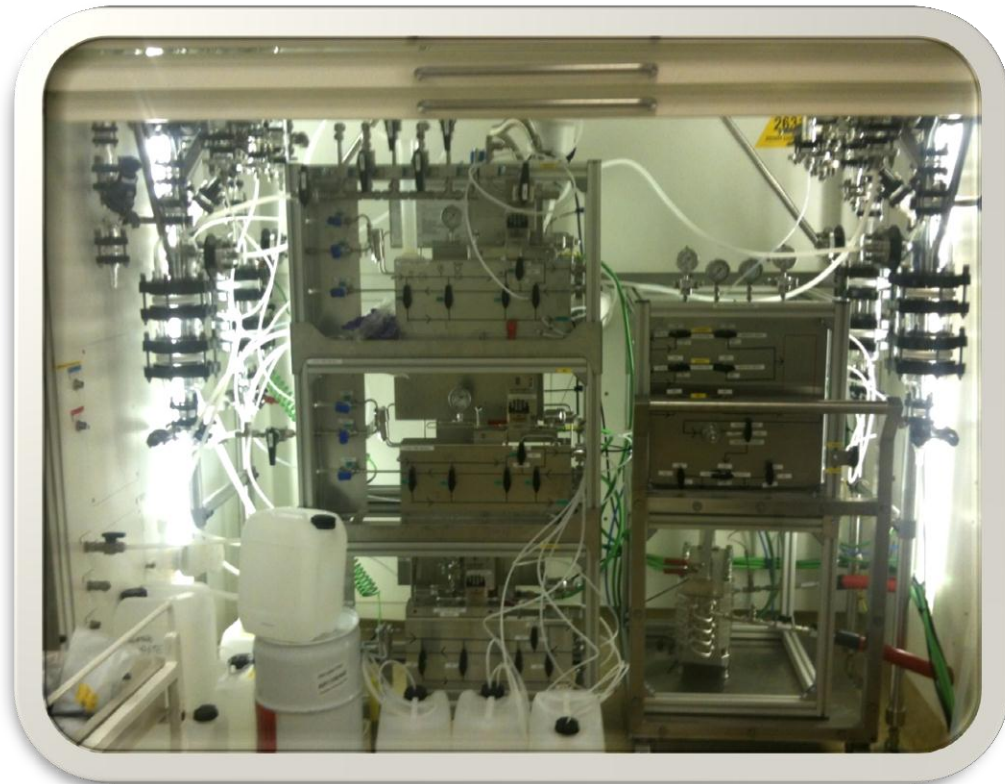
Progress

- Established in house capabilities for small scale continuous reactions.
- Developing in-house lab facilities for:
 - Liquid/liquid extractions
 - PAT for monitoring and control
 - Would like to develop gas/liquid capabilities in flow manufacture.
- Delivery on active drug projects
 - Active development projects are being evaluated on different equipment
 - Future Chem kit
 - Uniqsis Flowsyn
 - Screening established API processes for new opportunities
- Progressing understanding through European funded, multi-member collaborations, F3 and Synflow



Laboratory Scale Continuous Processing

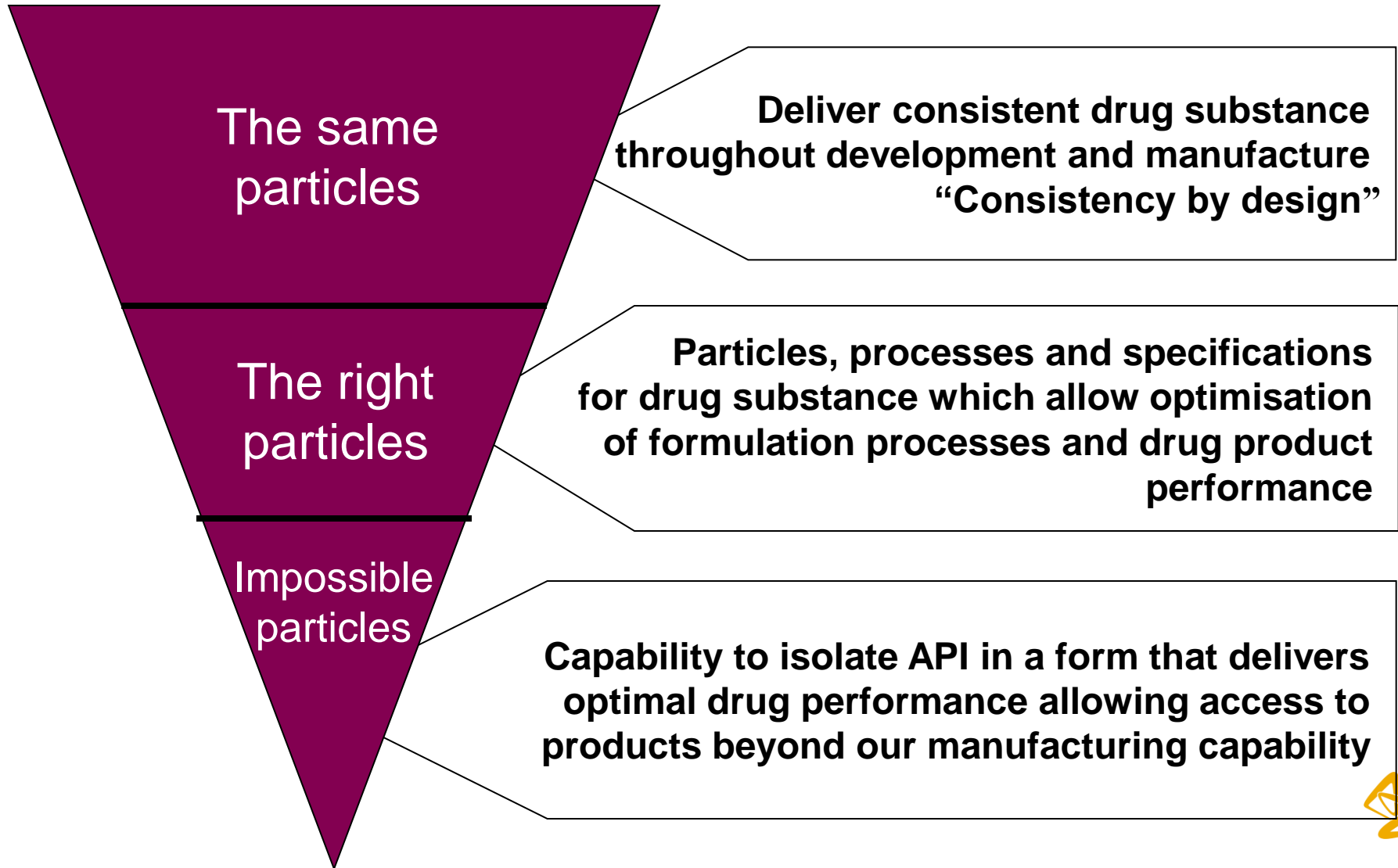
- GMP modular continuous processing equipment installed in LSL (Macc)
 - \$307k budget
 - European F3 project used to co-fund FTEs
- Alfa Laval continuous flow reactor used to deliver a clinical campaign
 - 1 kg processed in 7 hours
 - 74% yield (vs 60% batch) with improved quality



Continuous processing enables new operating conditions to be exploited



Design Right Particle



CMAC Summary

Making the most of the CMAC opportunity

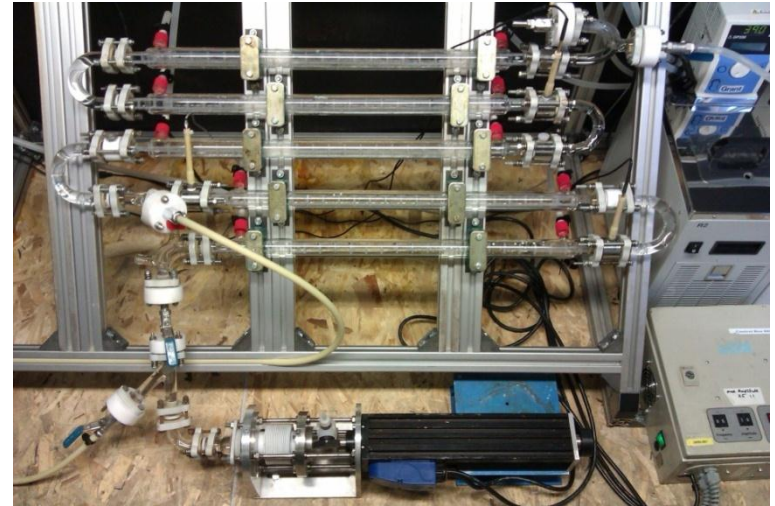
- AZ £1M is now potentially £40M + over the next 5 years
 - DTC starting in 2013 will provide 15 PhDs per year
 - Research foundations laid by all industrial partners
 - Includes learning from Novartis - MIT partnership
- Research focus is downstream of reaction (Workup, crystallisation, size reduction)
 - Aligned with Pharm Dev strategy and role of Physical Science
 - Flexible solids manufacture (Essential Science Area)
 - Continuous Chemical Processing (World Class Area)
 - CMAC research themes are being influenced by AZ capability gaps
 - Exquisite particle, workup
 - Quick wins – R&D has identified some projects
- Opportunity to link in drug product continuous processing work
 - Steering scope, proposing academic partners, assessing material variability.



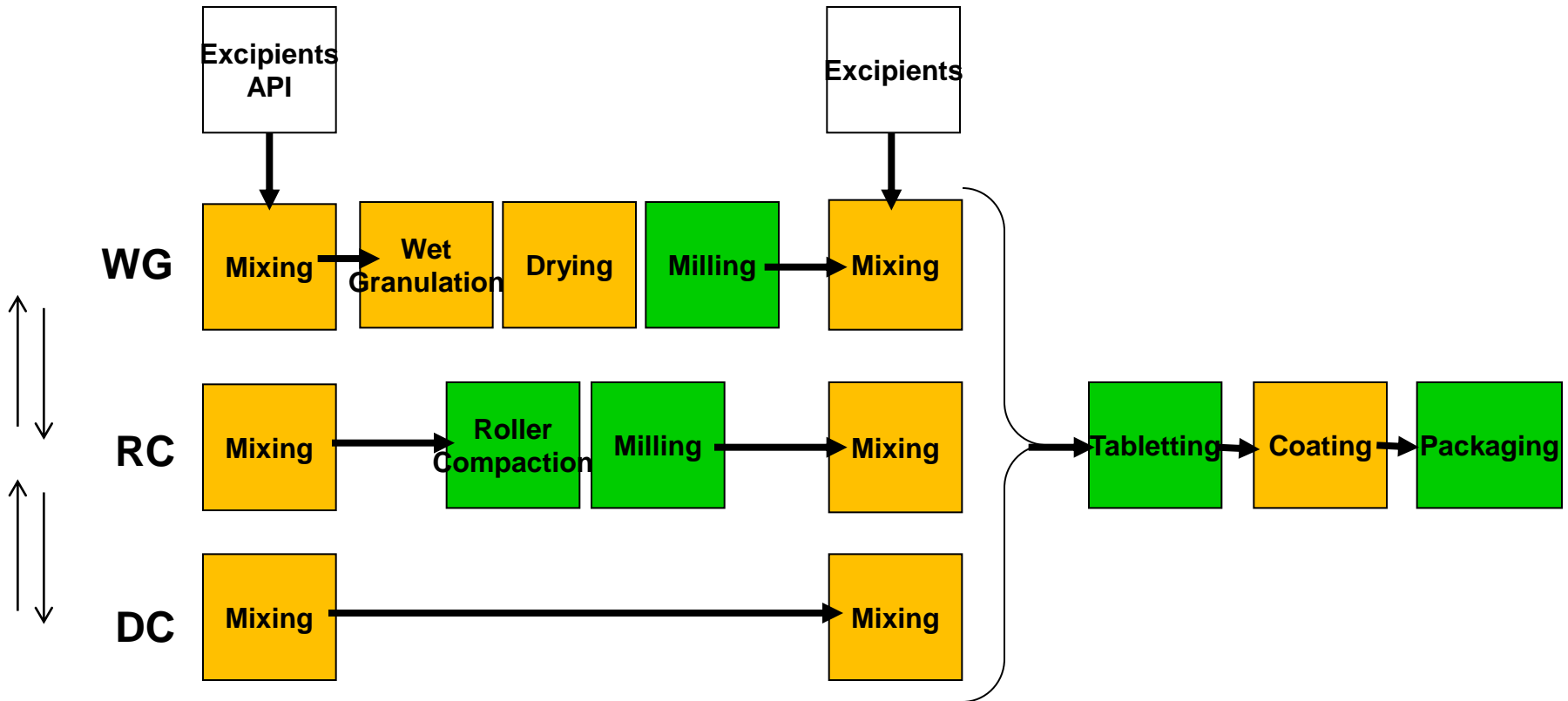
CMAC

Increased understanding

- Industrial baselining
 - shared learning and best practice to provide a solid foundation for the researchers to build on.
- “Simple” seeding project delivered significant learning for continuous crystallisation
- Able to progress “quick wins”



Tablet Manufacture: Continuous View



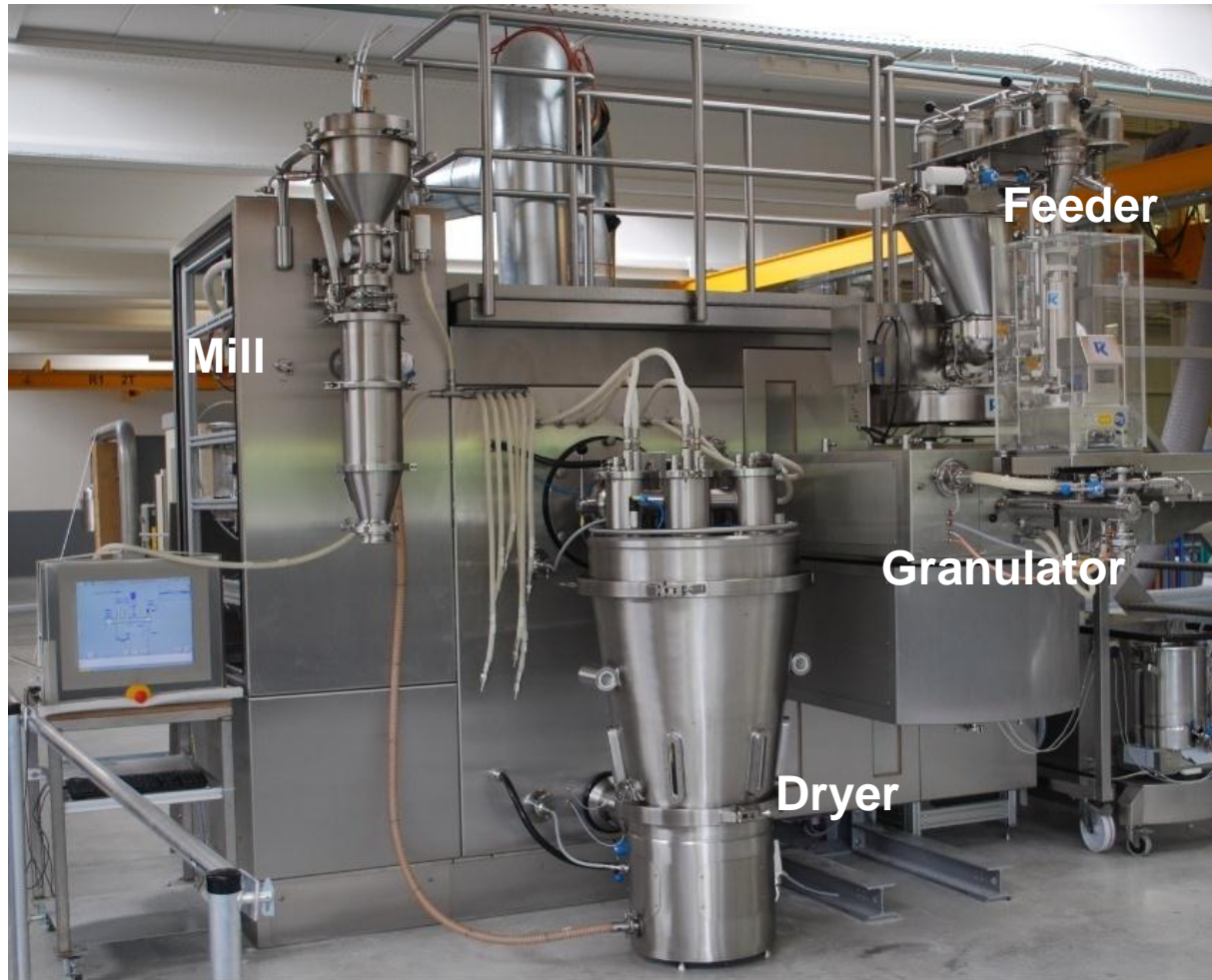
Unit operations which are continuous as long as they are fed with input material

Unit operations which can be continuous in the context of an appropriately designed process and control strategy

Opportunity for modular plug and play systems to exploit a range of manufacturing technologies

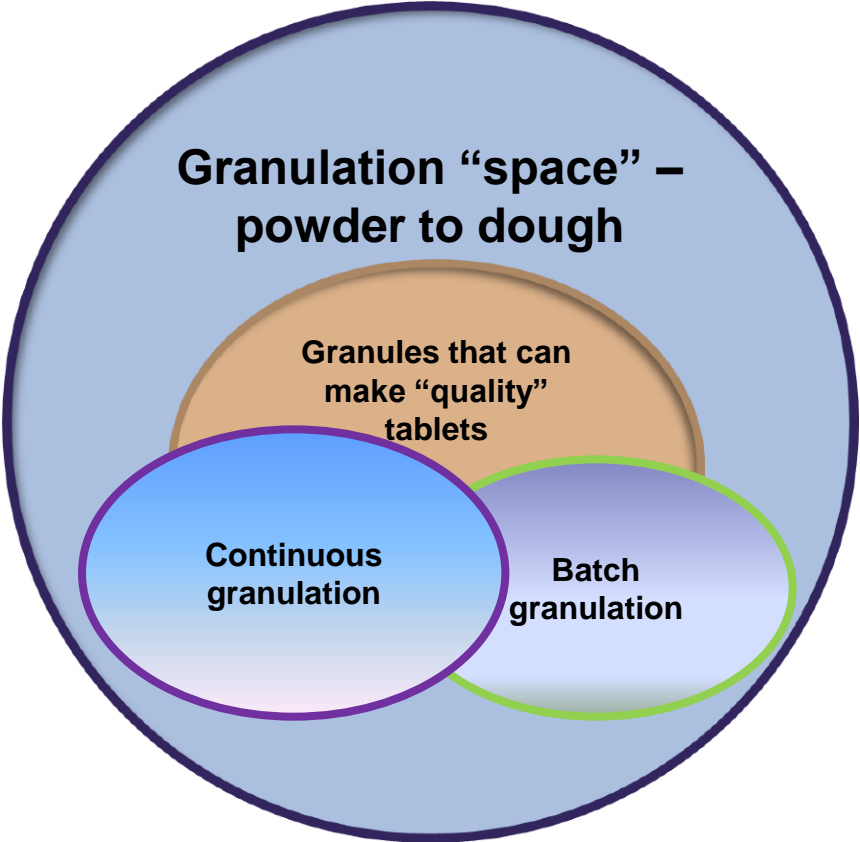
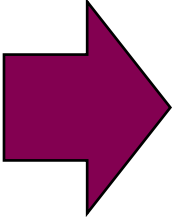
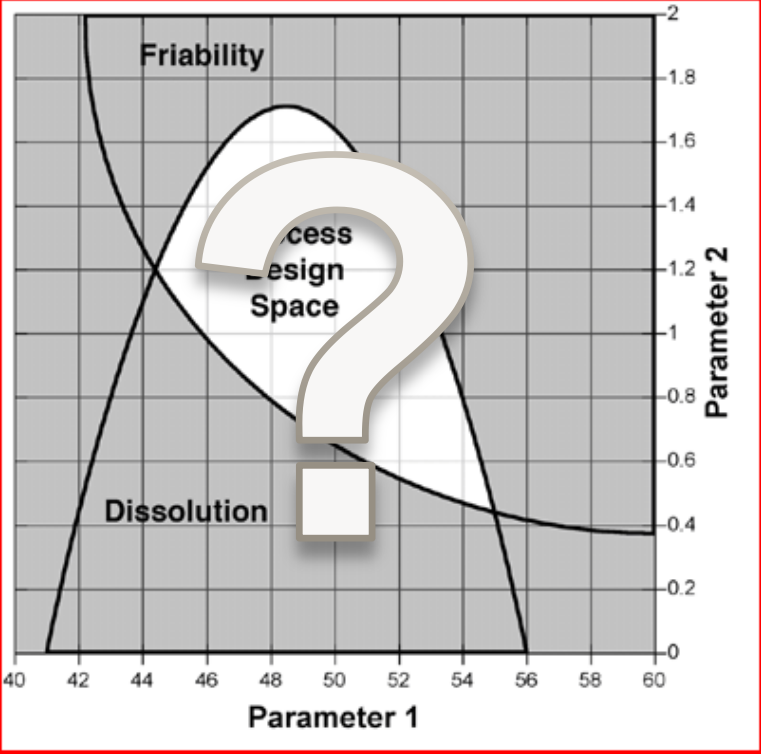


Lead technology for continuous wet granulation in AZ



* Thompson M.R. and Sun J. 2010. J.Pharm.Sci. 99, 4, 2090-2103.

Understanding Continuous vs Batch?



A Role for CMAC

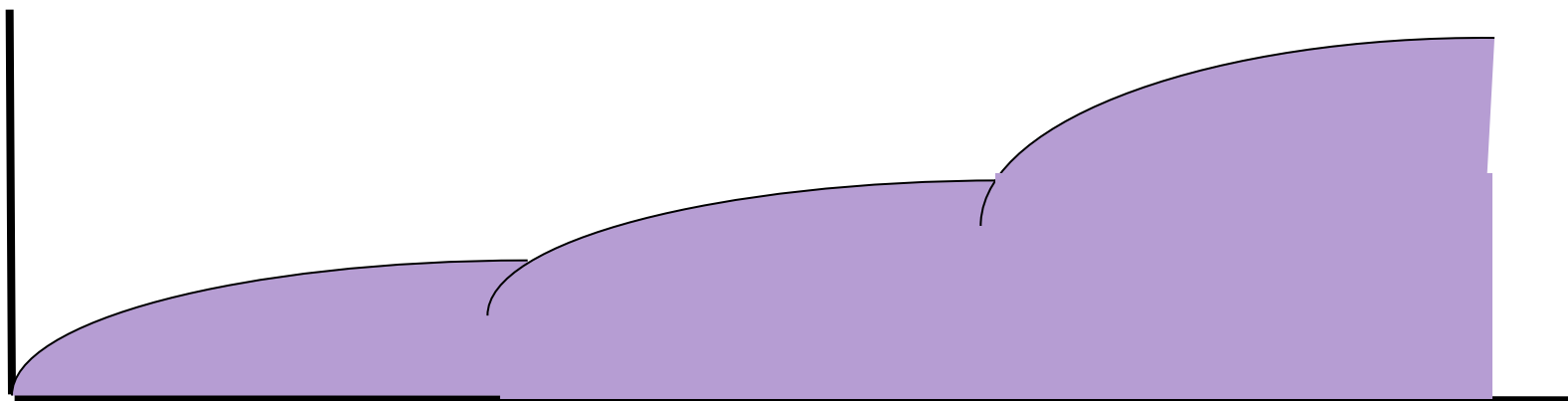
Addressing the challenges

- Increase knowledge
 - Generating mechanistic insight for immature technology (e.g. work up, OBC)
- Experience and solve technical challenges on real or good model compounds
 - Overcomes inertia and resistance to change.
- Develop capability
 - Continuous operation demonstrating consistent product with varying batch size
 - Process analysis and advanced control
 - Powder handling and feeding
 - Pumping
 - Cleaning
- Understand and address the concerns of regulatory agencies
- Ensure freedom to operate



A role for CMAC

The innovation pathway for continuous processing



Horizon 1

‘Superior Execution’

- Build capability in Development
- Initiate use of established technology in projects
- Generate mechanistic insight

Need - Experience

Horizon 2

‘Positional Advantage’

- Establish commercial manufacturing capability
- Establish control strategies by exploiting PAT and advanced control
- Successful regulatory approval of continuous processes

Horizon 3

‘Insight & Foresight’

- Broader application
 - New value opportunities
- Real Time Release*
Shortened lead time
Smaller volumes
- End to end manufacture (substance through to pack)



Summary

- Continuous manufacture is an attractive value proposition for the Pharmaceutical Industry.
- There are substantial challenges; technical, commercial and cultural.
- AZ is working with multiple partners across the whole scope of Pharmaceutical process development to establish continuous processing.
- This is a precompetitive area; sharing knowledge and resources will result in more rapid, cost effective progress.
- CMAC has an influential position given its scope, funding and capability to address the challenges and “Accelerating the adoption of continuous manufacturing and crystallisation processes systems and plant for the production of high-value products to higher quality, lower cost, more quickly and more sustainably.”



Acknowledgements

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