Breakthroughs that change patients' lives

Drug Product Continuous Manufacturing

Daurismo™ case study

Dr. Meike Vanhooren
Senior Director
Global Chemistry, Manufacturing & Controls

Overview

Drug Product Continuous Manufacturing

- Continuous Manufacturing Enabling Acceleration (Video)
- Case Study - Daurismo™

Continuous Manufacturing is ….

- the future standard for solid oral dosage forms with greater process understanding and control
- redefining how drugs are produced
- a faster, more precise and reliable manufacturing approach

- **Continuous Manufacturing is enabling Accelerated Development**

What does that mean?

Source: youtoube.com „PCMM Pfizer“

- https://www.youtube.com/watch?v=j16D2GMVaEk

Glasdegib (Daurismo™)

NDA filing accelerated by more than 3 years!

2013

- Identified as a good candidate for the continuous manufacturing pilot

2016

- Clinical “End of Phase 2” meeting with FDA led to opportunity to file NDA with Phase 2 data

2018

- NDA filing accelerated by more than 3 years (from 2Q2021 to 1Q2018)
- Phase 2 study used glasdegib diHCL; Phase 3 & registration uses glasdegib maleate

Daurismo™ (Glasdegib) Tablets

Drug Product Overview

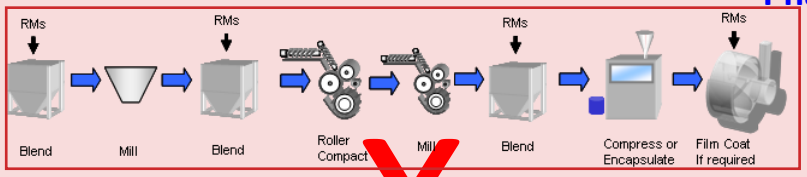
- Direct Compression using
  Portable, Continuous, Miniature & Modular (PCMM) technology for tablet cores and batch film-coating
- Product development accelerated by more than 3 years

PCM&M Platform Technology

Current State
(dry granulation / roller compaction)

Drug Product Quantities

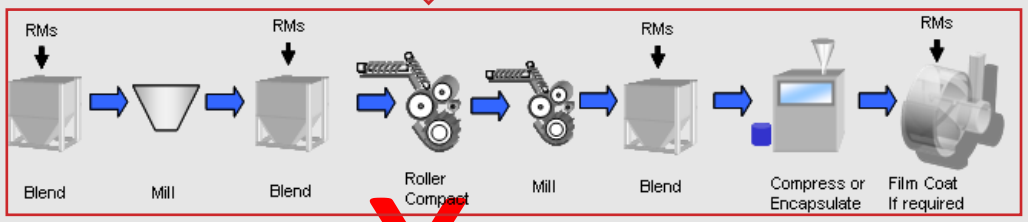
Phase IIB Clinical Supplies



<10 kg

Tech Transfer & Process Scale Up

Phase III Clinical Supplies



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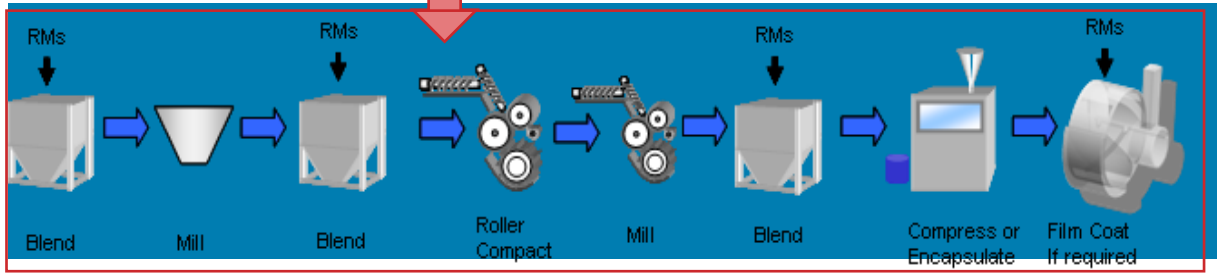
Tech Transfer & Process Scale Up

Commercial Supplies



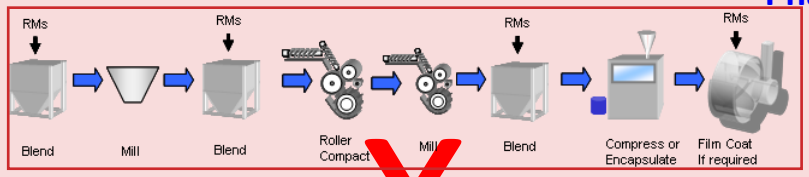
100 to 1000 kg

PCM&M Platform Technology

Current State
(dry granulation / roller compaction)

Drug Product Quantities

Phase IIB Clinical Supplies



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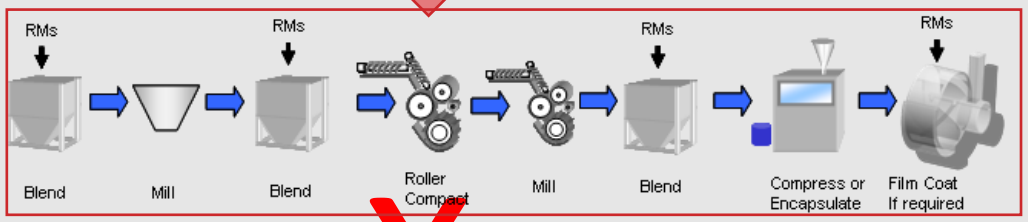
Tech Transfer & Process Scale Up

Phase III Clinical Supplies



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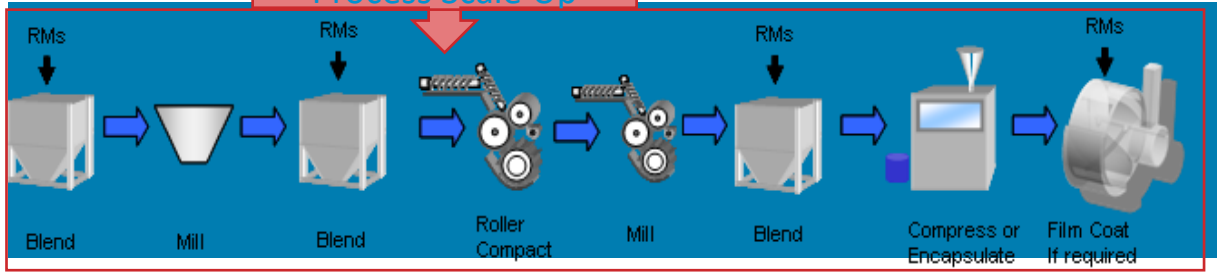
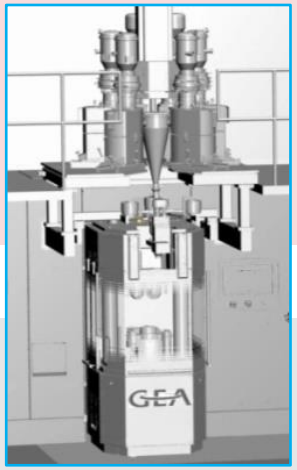
Tech Transfer & Process Scale Up

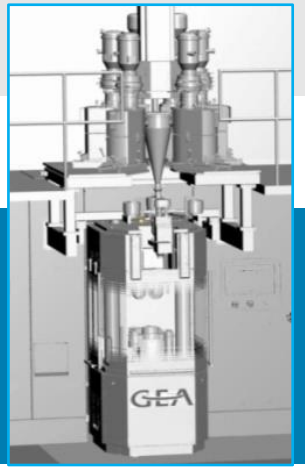
Commercial Supplies

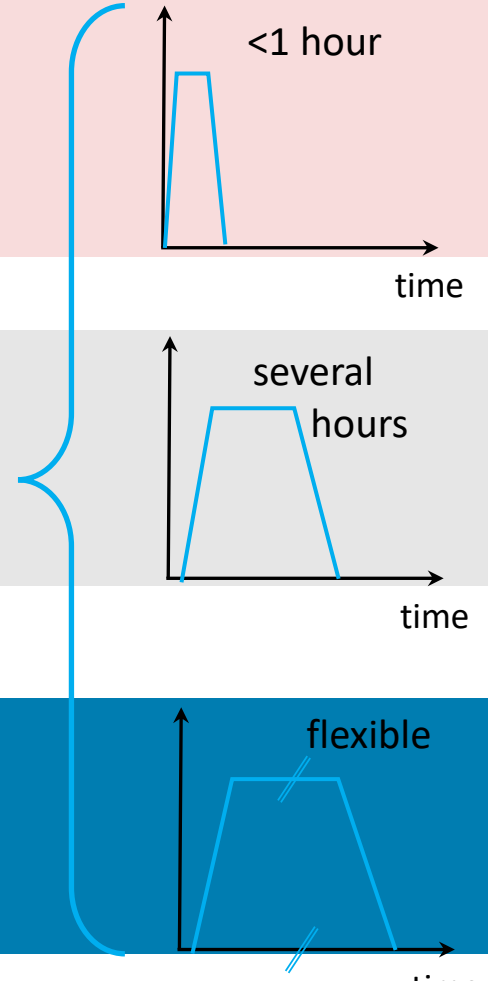


100 to 1000 kg

Future State
(dry blend / direct compaction)





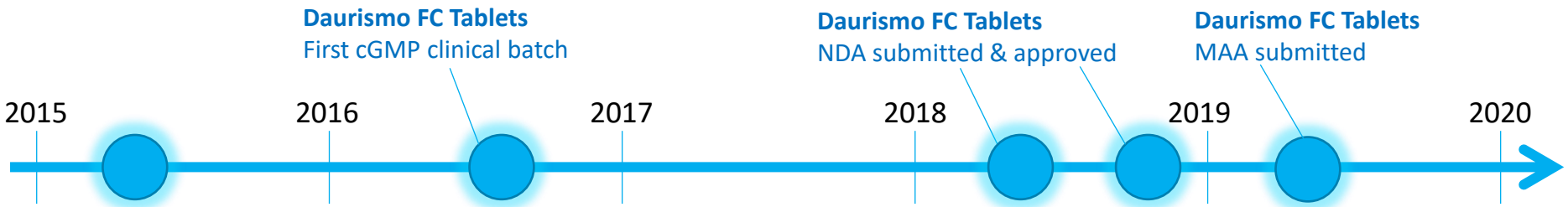


PCMM Technology Investments across Pfizer

Groton, USA
cGMP clinical and commercial

Sandwich, England
development

Freiburg, Germany
cGMP clinical and commercial



Pfizer
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Agency Meetings

Overview of FDA Interactions

- 2017:
  - Accepted into FDA ETT Program
  - 3 F2F CMC Type C meetings
- 2018:
  - F2F CMC AOM (PCMM video)
  - Met with Reviewers/Inspectors @ Groton PAI

NDA Approved Nov 21st

PDUFA Dec 27th

Groton PAI July 9th

NDA Apr 27th

32 cmc queries;
8 related to PCMM or NIR

Continuous Manufacturing

Regulatory Criteria

- Definition of a Batch
  - ❑ Required to file a “batch size”
  - ❑ Characterize run time (xx hrs) vs. fixed volume (# kgs)
  - ❑ Justify max run time w/data
- Lot Traceability
  - ❑ Trace raw material pedigree
- Batch Uniformity
  - ❑ On-line analytics critical to demonstrate batch consistency
- Process Upsets
  - ❑ Demonstrate process perturbations are managed*

*Includes disposition of material already produced, investigation steps, process restart procedures, etc.

Regulatory Considerations

Definition of Batch:

- Batch size is being determined by the weight of in-going raw materials

NIR Model Maintenance:

- Pfizer's position is that this should be handled by company's Pharmaceutical Quality System and notification to an approved application should not be necessary
- FDA/Pfizer negotiated maintenance plan during review; update model maintenance activities in AR for most cases, no need to submit data

Contingency Plans:

- Should be identified in case NIR/PAT controls are not available
- FDA approved Pfizer's stratified sampling plan and offline HPLC testing in NDA

Technology Transfer:

- Pfizer's position is that there should be significantly less data required for tech transfer of identical continuous manufacturing units
- Pfizer decided to include Freiburg process validation report & 3m stability data to in PAS

Regulatory Considerations (cont)

Process Validation:

- Three Batch Process Validation is required by some markets, but 3-stage and concurrent approaches should also be accepted
- FDA agreed to Pfizer's proposed 3-stage validation approach but Pfizer decided to use traditional 3 batch validation for glasdegib
- Reference: FDA's Guidance for Industry, Process Validation: General Principles and Practices (January 2011).
  - Stage 1 – Process Design
  - Stage 2 – Process Qualification
  - Stage 3 – Continuous Process Verification

Summary

- Pre-Filing Interactions w Regulators are crucial

- The PCMM technology is changing the paradigm for developing and manufacturing solid oral dosage forms
  - Early signs of delivering on speed to market
  - Continuing to gain trust and confidence in the technology
    - Guard against over-conservatism
  - Continue to explore opportunities for increased flexibility
    - Model updates, extension of run times (i.e. increase of scale), site transfers with like-for-like equipment

Acknowledgments

- Colleagues in
  - Worldwide Research & Development,
  - Pfizer Global Supply,
  - Quality,
  - Regulatory,
  - and more

- *Special Thanks to Roger Nosal, John Groskoph, Tom Garcia, Suzanne Mayr, Julia Claus, Hong Jiang, Dan Blackwood, Patrick Daugherity, Julie Wood, Angela Liu and many other!*

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