Timescales for Change – A Look at Innovation in the Pharmaceutical Industry

3rd FDA/PQRI Conference on Advancing Product Quality

23 Mar 2017

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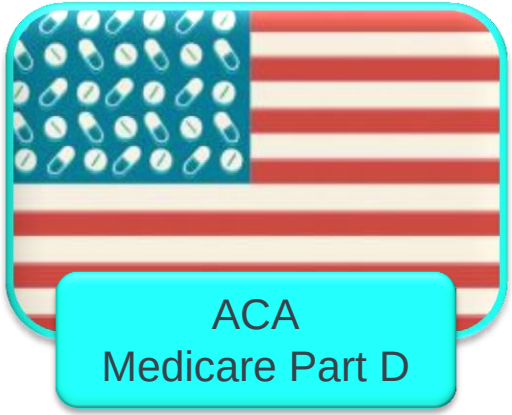
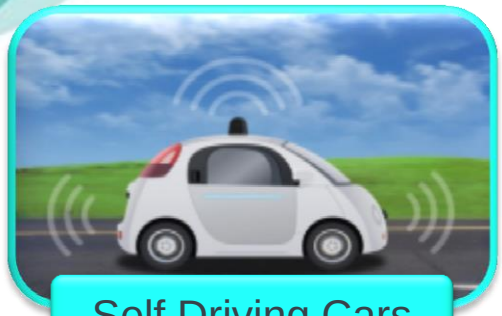
Global Pharmaceutical Commercialization

Merck & Co., Inc.

How has the world changed in the last 15 years?

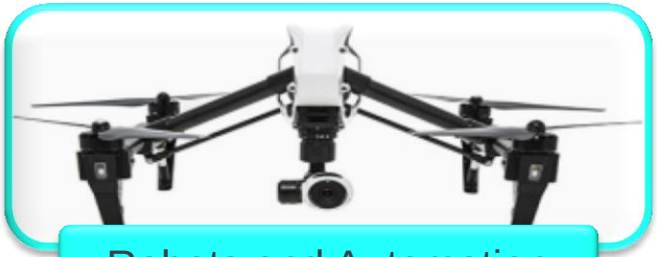


How will the world change in the next 15 years?



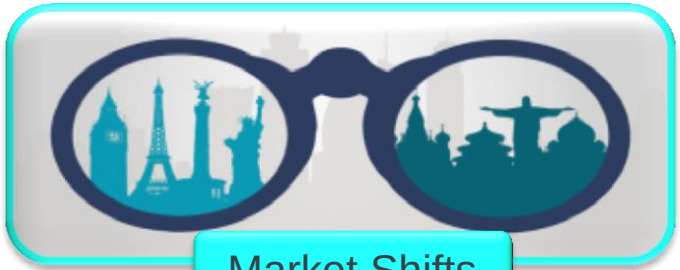
Self Driving Cars

Big Data



Robots and Automation

Artificial Intelligence

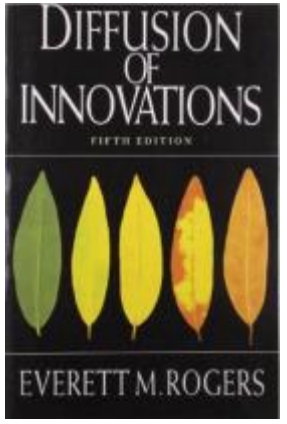


Market Shifts

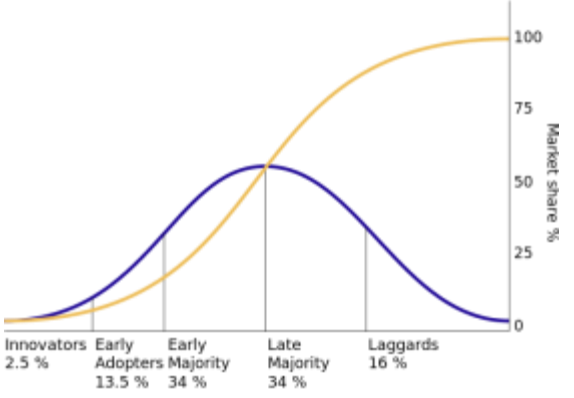
Individualized Medicine

Characteristics of Innovations

- Potential adopters evaluate an innovation based on
  - Relative advantage
  - Compatibility with the pre-existing system
  - Complexity or difficulty to learn
  - Ability to test
  - Potential for additional uses
  - Observed effects
- Speed of adoption is related to non-linear summation of these factors

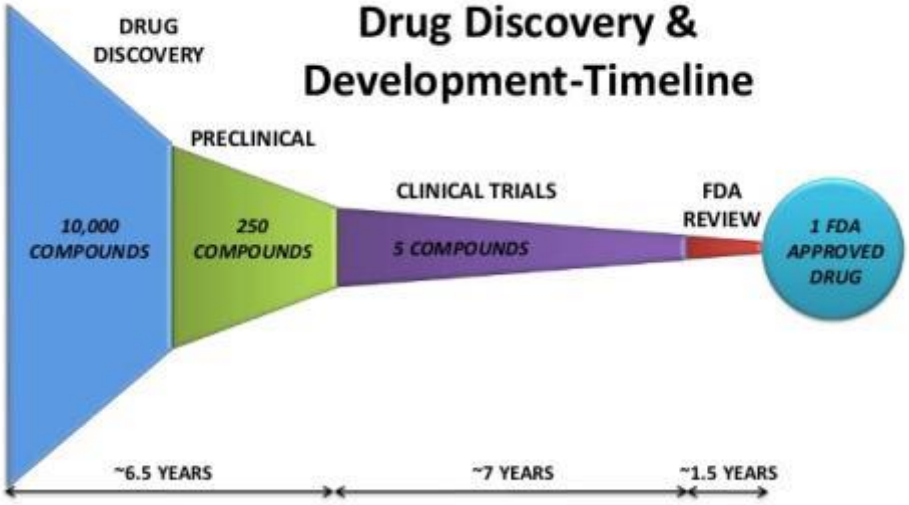


Rogers, *Diffusion of Innovations*, 5th Edition, (2003)



https://en.wikipedia.org/wiki/Diffusion_of_innovations

Innovation in Medicine and Manufacturing are Similar



Case Study:
Poorly Soluble Small Molecule Drugs

PROBLEM

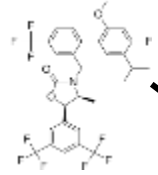
Many APIs have poor solubility

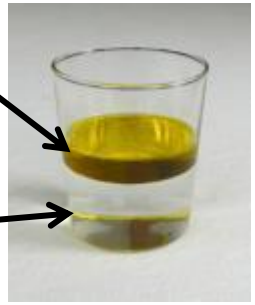
CONSEQUENCE

Body doesn't absorb drug from conventional dosage form

NOVEL SOLUTION

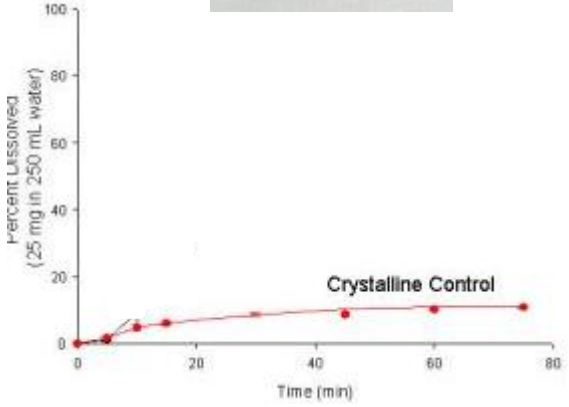
Amorphous solid dispersions enhance dissolution





Oil

Water



Hot Melt Extrusion (HME) Overview

- Hot melt extrusion applications:
  - Generating amorphous solid dispersions
    - solubility enhancement
    - food effect mitigation
  - Controlled release
  - Taste masking
  - Abuse-deterrence

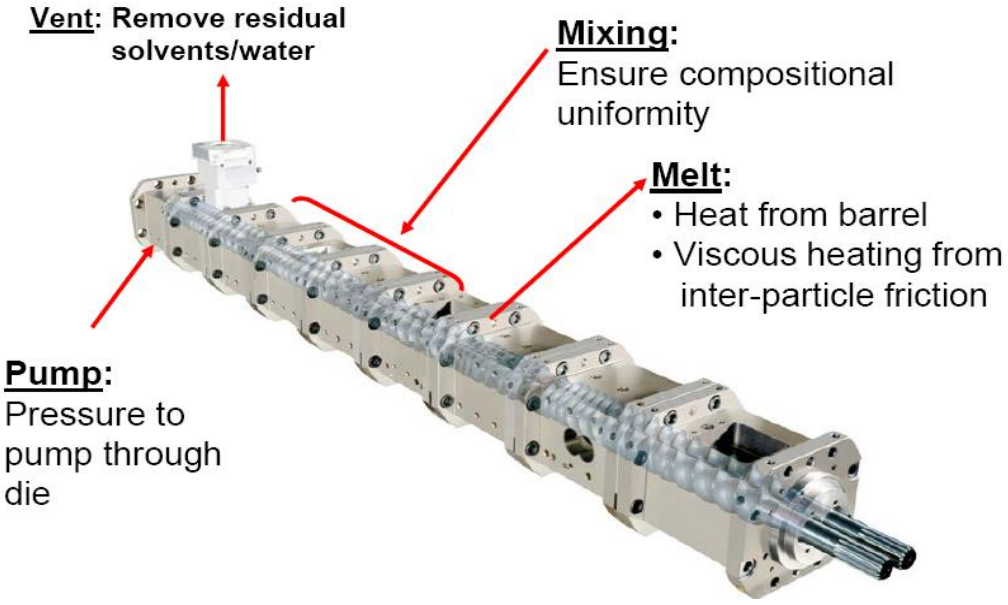
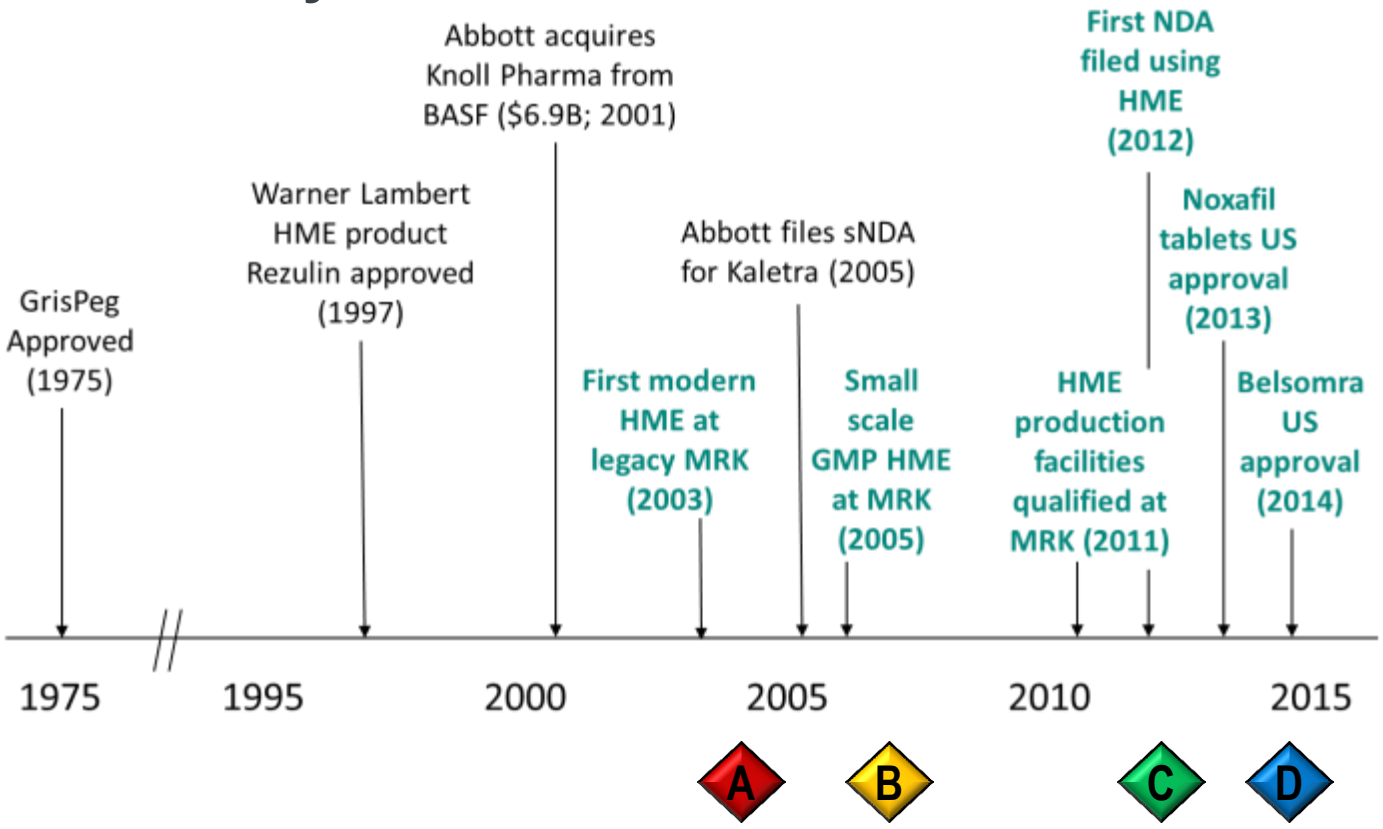
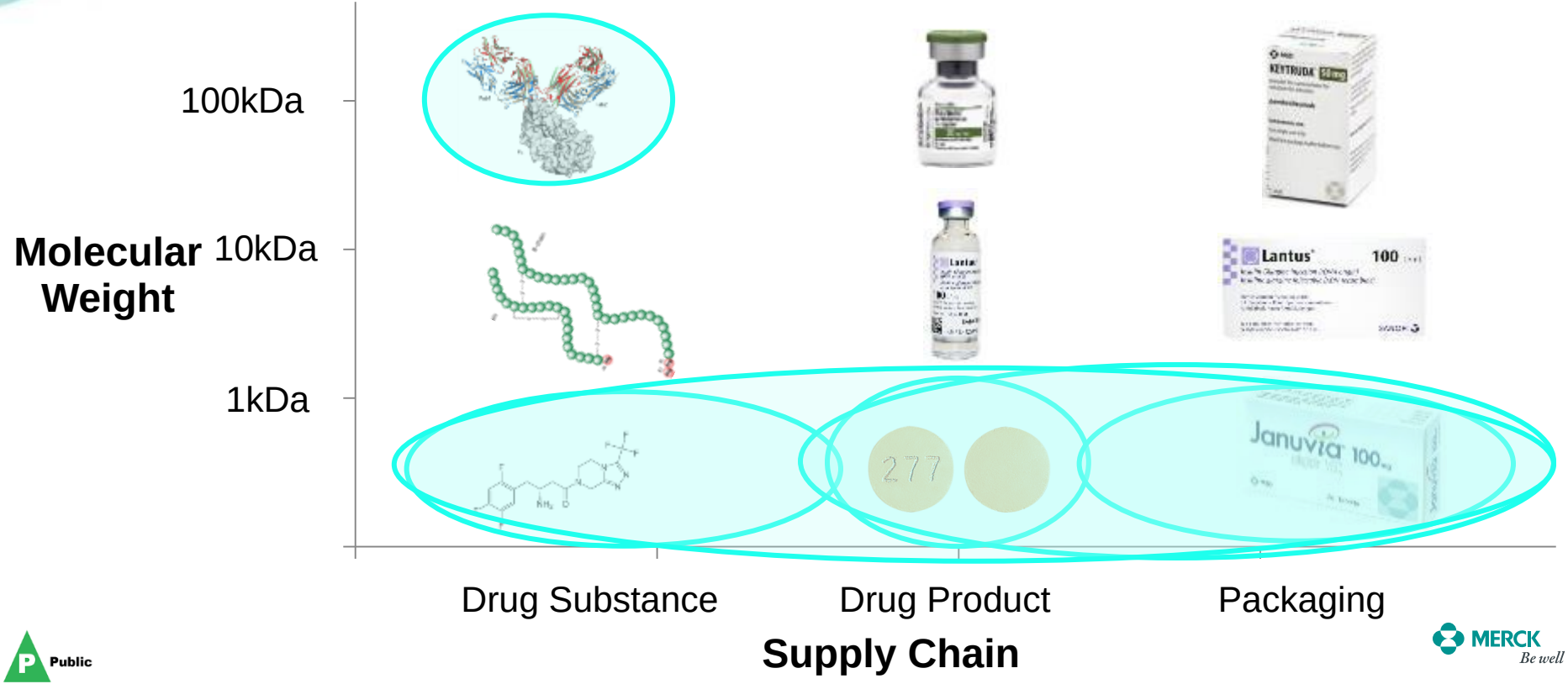


Image courtesy of American Leistritz Extruder Corp

Timeline of Solid Dispersions and HME in Industry and Merck

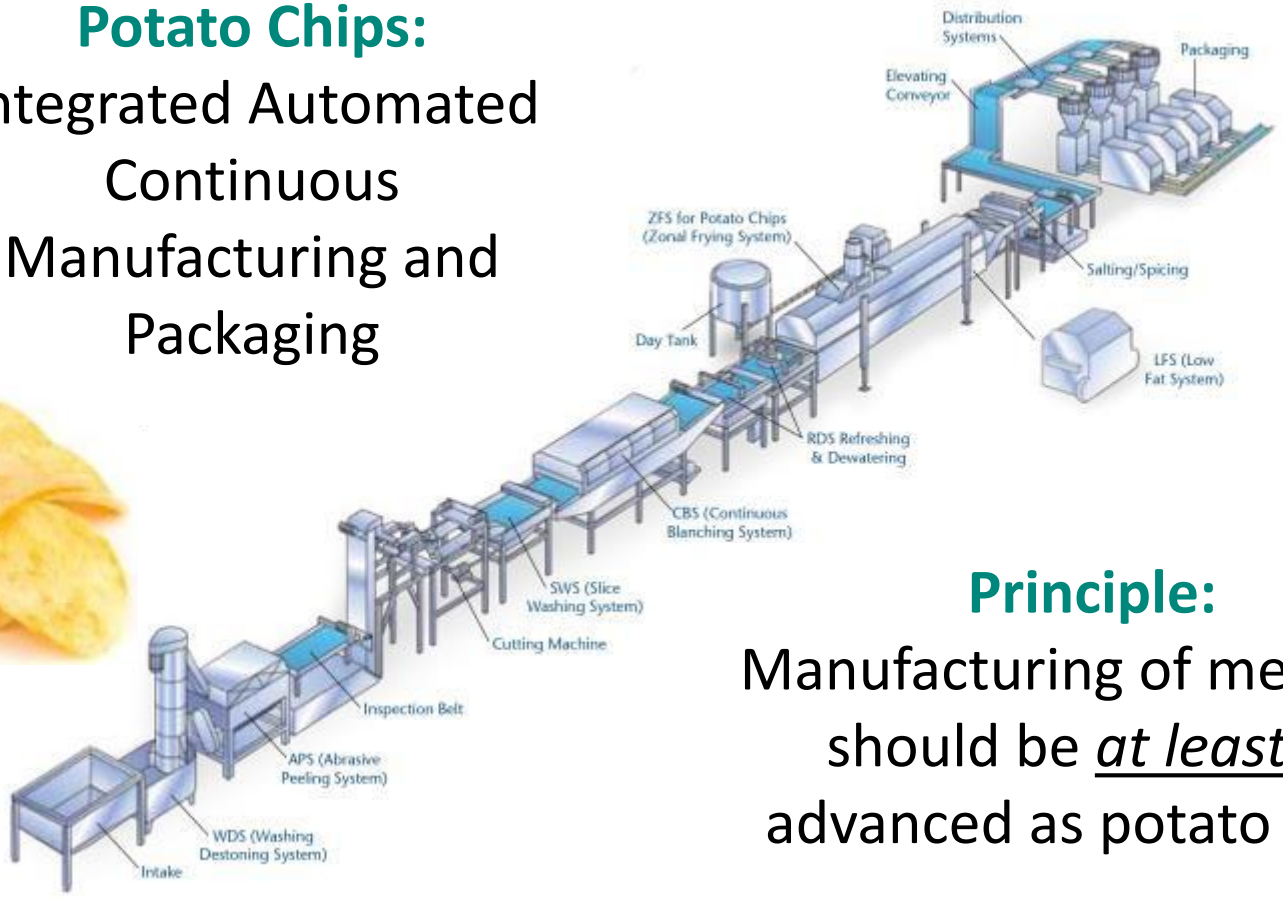


Applications for Continuous Manufacturing



Potato Chips:

Integrated Automated Continuous Manufacturing and Packaging



Principle:

Manufacturing of medicine should be *<u>at least</u>* as advanced as potato chips

http://www.sanco-indonesia.com/media.php?id=32&product=continuous-fryer

Continuous Manufacturing Vision:

To create a small, flexible, replicable, multiproduct facility operating in sync with customer demand

Proof of Operations:

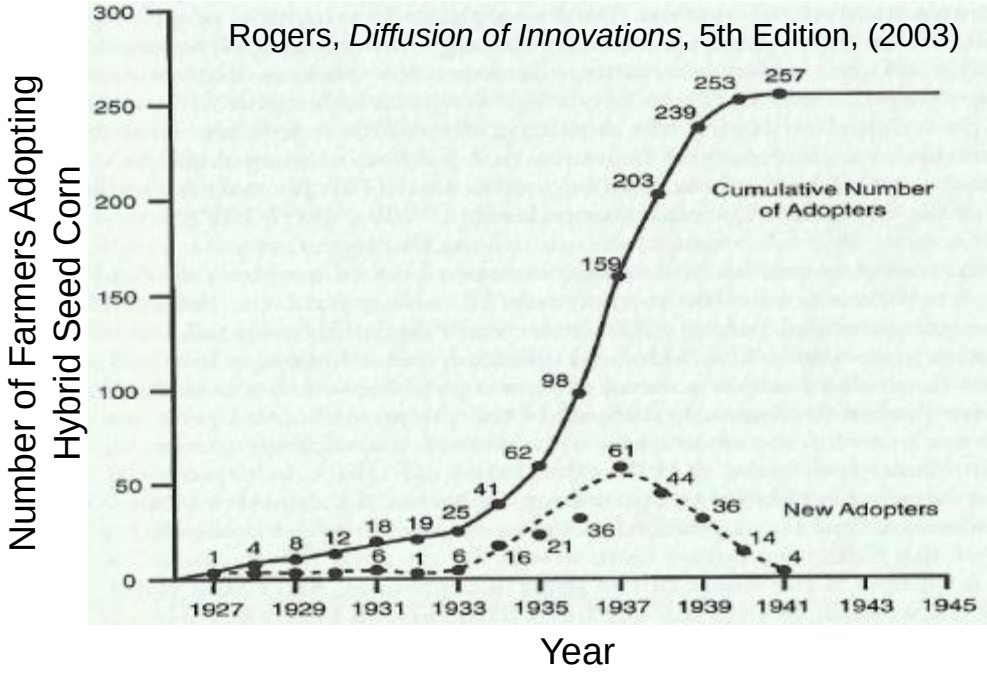
Merck's Continuous Direct Compression + Film Coating Facility

- **~1 billion tab/yr** to serve US & other markets
- **< 90 day lead time** formulation to patient
- **Production at rate of consumption**
- Footprint **~⅓ the size** of a traditional facility
- Template for the **future**

Iowa Hybrid Corn Study

In 1943, Ryan and Gross measured number of adopters of hybrid seed corn in two Iowa communities

- Adoption of a new idea results from information exchange through interpersonal networks
- Adoption rate incubated slowly, then accelerated
- Degree of innovativeness is normally distributed
- To reach 95% completion took about 13 years



Time Constants for Continuous Manufacturing

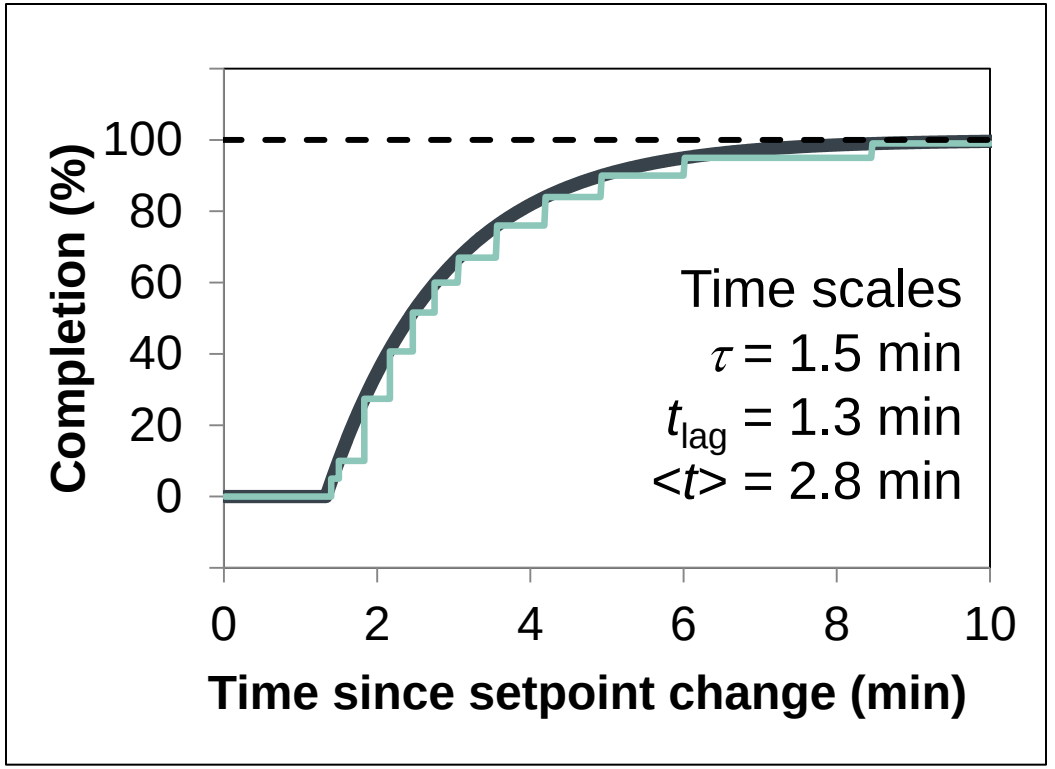
After a setpoint change

- There will be a time lag, t_{lag}, before any change is seen
- After t_{lag}, rapid movement will be seen
- To reach 95% completion takes $t_{lag} + 3\tau$

For new tech in pharma,

- $t_{lag} \approx 12$ yr
- $\tau \approx t_{obstacles} + t_{clinical} + t_{approval}$
- $\tau \approx 1 + 4 + 2$ yr $= 7$ yr

95% complete ≈ 33 years



Where have we been, where are we going?

2030

2025

ICH countries acceptance of CM

2020

Most of industry invested in CM

2015

PREZISTA® darunavir

ORKAMBI

2010

Industrial lab proof of concept & development

ICH Q8 – Pharmaceutical Development

2005

Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

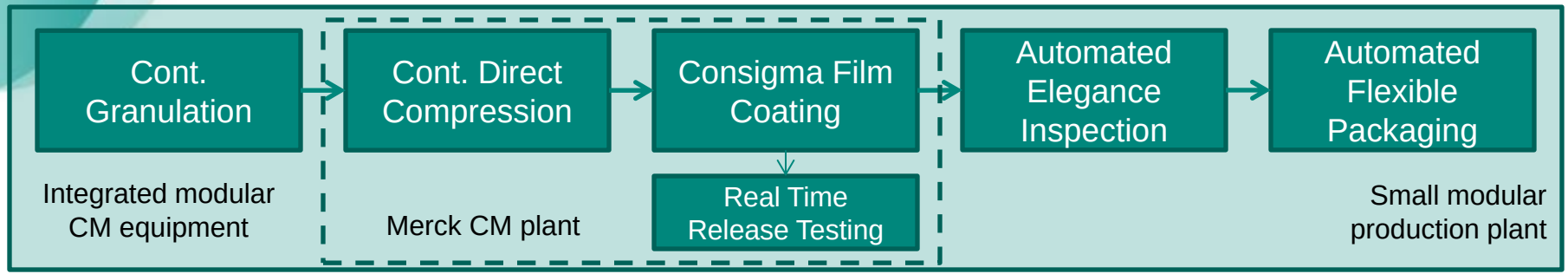
PAT guidance for industry (FDA)

2000

Academic research, C-SOPS

Computer + internet revolution

Vision for 2030



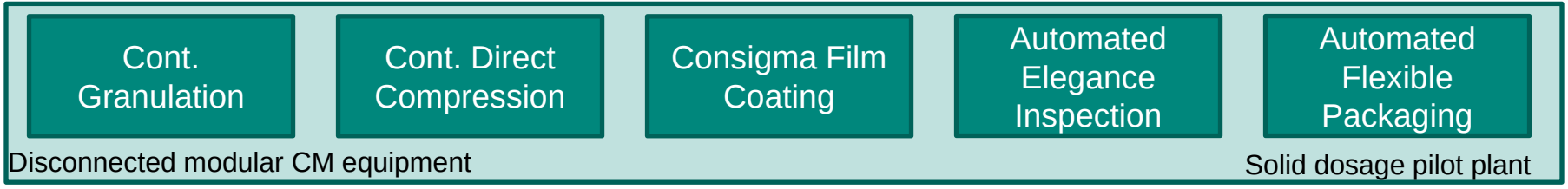
In the factory

- Fully integrated formulation, packaging and release
- Lead time so low that 2 year shelf life is never needed
- Batch sizes so small that you can pack for an individual pharmacy
- Changeover times so fast that true SMED is achieved
- Information flow so efficient that we can truly make to order
- Footprint so small that we can use portable, modular construction
- Plant build so fast that a new facility is completed in a year
- Automation so robust that true ‘lights out’ manufacturing is achieved
- Regulatory confidence that any product could be approved using CM & RTR in any market
  Information flow to regulators allows virtual, risk based inspections

Vision for 2030

In the pilot plant

- Lead time so low that batch start to clinical delivery <30day
- Dynamic experimentation enables us to move beyond the DoE
- Data collection so robust that design space established in 1 day of experimentation
- Formulation screening uses automated algorithms
- Min batch sizes so small that CM work can begin in Phase I
- Integrated PAT enables process understanding and RTRT in Phase II
- Equipment identical to commercial plant so tech transfer is trivial
- Technology confidence that any product could be produced via CM



What People Say Are the Obstacles to Innovation

Program Risks

- Not sure if this will ever become a product…

Program Timelines

- Not sure if we have time for innovation now…

Regulatory Risks

- Not sure if regulators will approve this…

Cultural Inertia

- Not sure if we should do something differently than before…

Business Benefit

- Not sure if we can easily quantify cost savings, risk reduction…

Budgetary Constraints

- Times are tight, so we'll innovate next week / quarter / year

Rewards and Recognition

- Not sure if I'll be recognized for innovative work

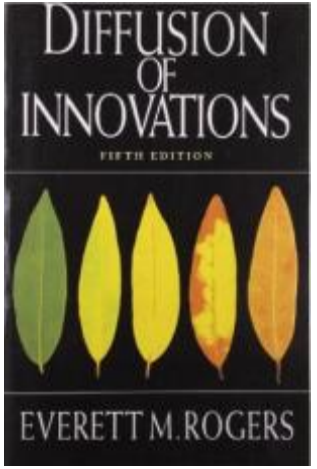
Sponsorship

- Am I even allowed to innovate?

…and I don't have time!

Summary & Conclusion

- Relative benefits and obstacles for CM adoption are in the eye of the beholder
- Compatibility with pre-existing systems and difficulty to learn are still being finalized
- Rate of diffusion is dependent on the social construct of our industry and our willingness to share experiences
- The innovators and early adopters amongst us will be most likely to win the largest benefits by shaping the way we adopt new technology



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Questions?

Acknowledgements

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