Breakthroughs that change patients' lives

PCMM and Beyond – Next Gen Innovation for Solid Oral Dosage Forms

Daniel Blackwood, Research Fellow
Pharmaceutical Sciences – Small Molecule

Presentation Outline

Innovation Themes for Small Molecule Solid-Oral Drug Products

- Facility and Process Innovation Drivers

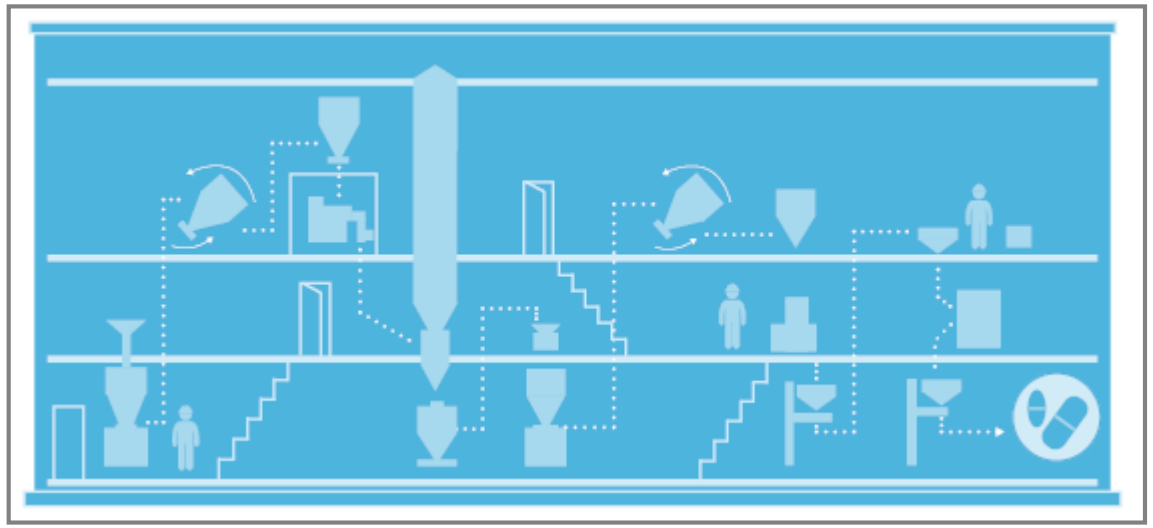
- Current Landscape for Drug Product

- Technology Implementation Challenges and Incremental Innovation Cycle

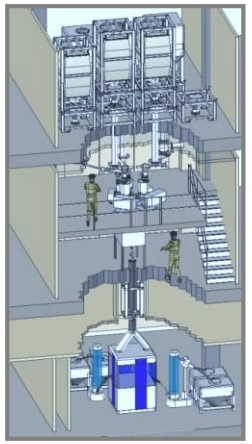
- Future Innovation

Decade(s) of Facility & Process Evolution

Traditional Drug Product Facility



High Volume Continuous Facility



Integrated Development & Manufacture Facility

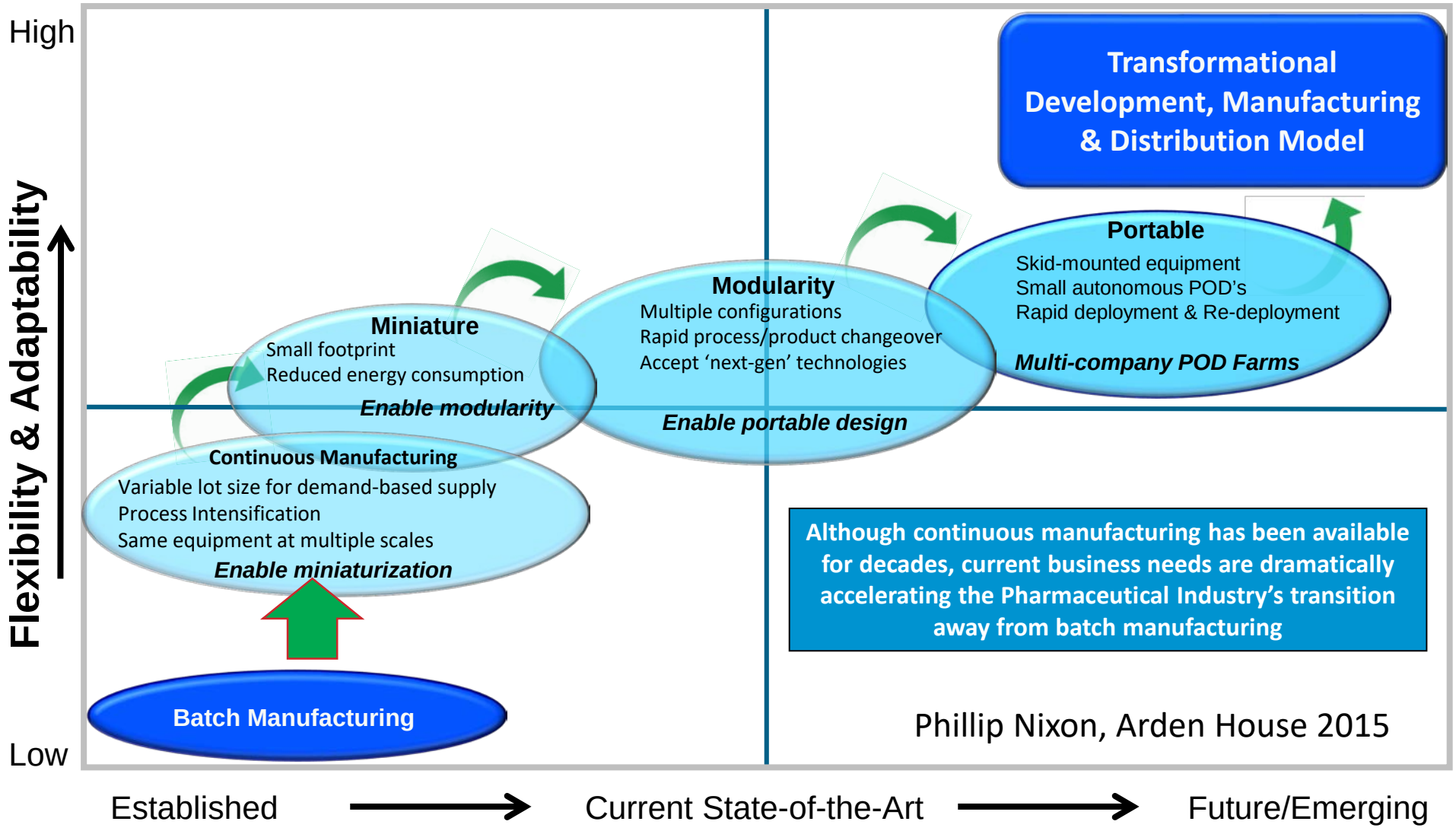
Blockbuster Medicines Era
Low Organizational Risk Tolerance
Capacity-driven, "Like-for-Like" replication of existing DP trains

Loss of Exclusivity/ Loss of Revenue/ Excess Capacity

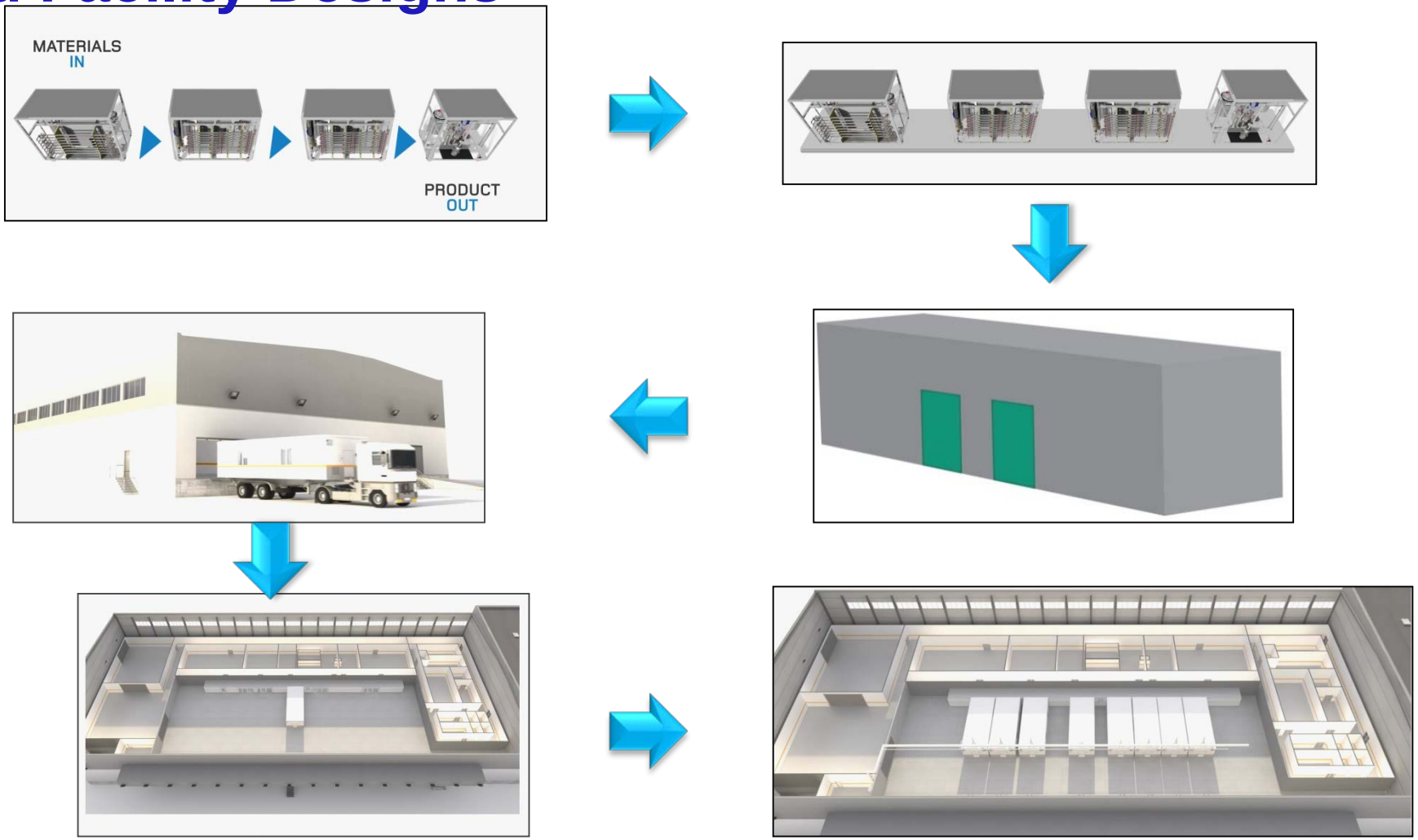
Personalized Medicine Era
Opportunity - Need for speed to market

Pfizer | Breakthroughs that change patients' lives

Continuous Manufacturing Initiates a Cascade of Transformational Technology Advances



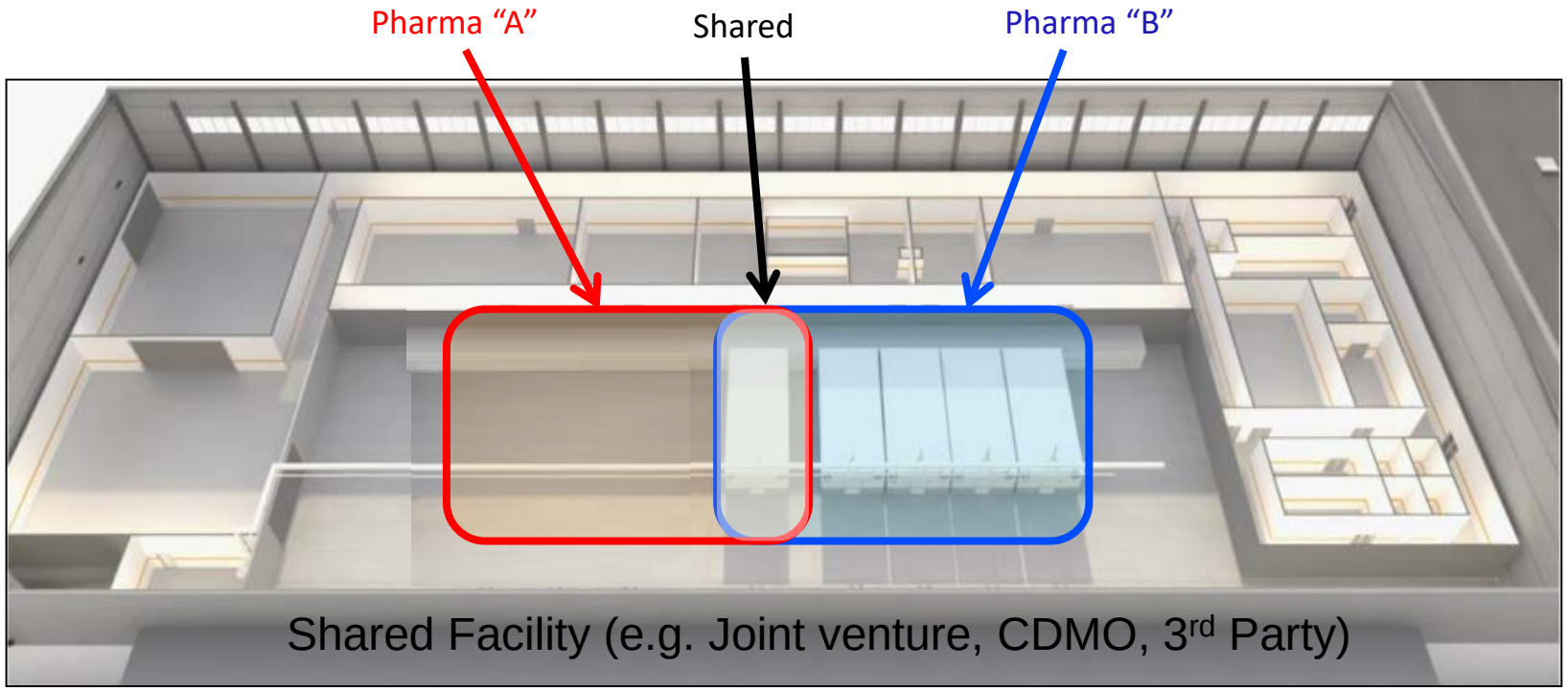
Some Emerging Opportunities – Portability (Rapid Deployment) POD Based Facility Designs



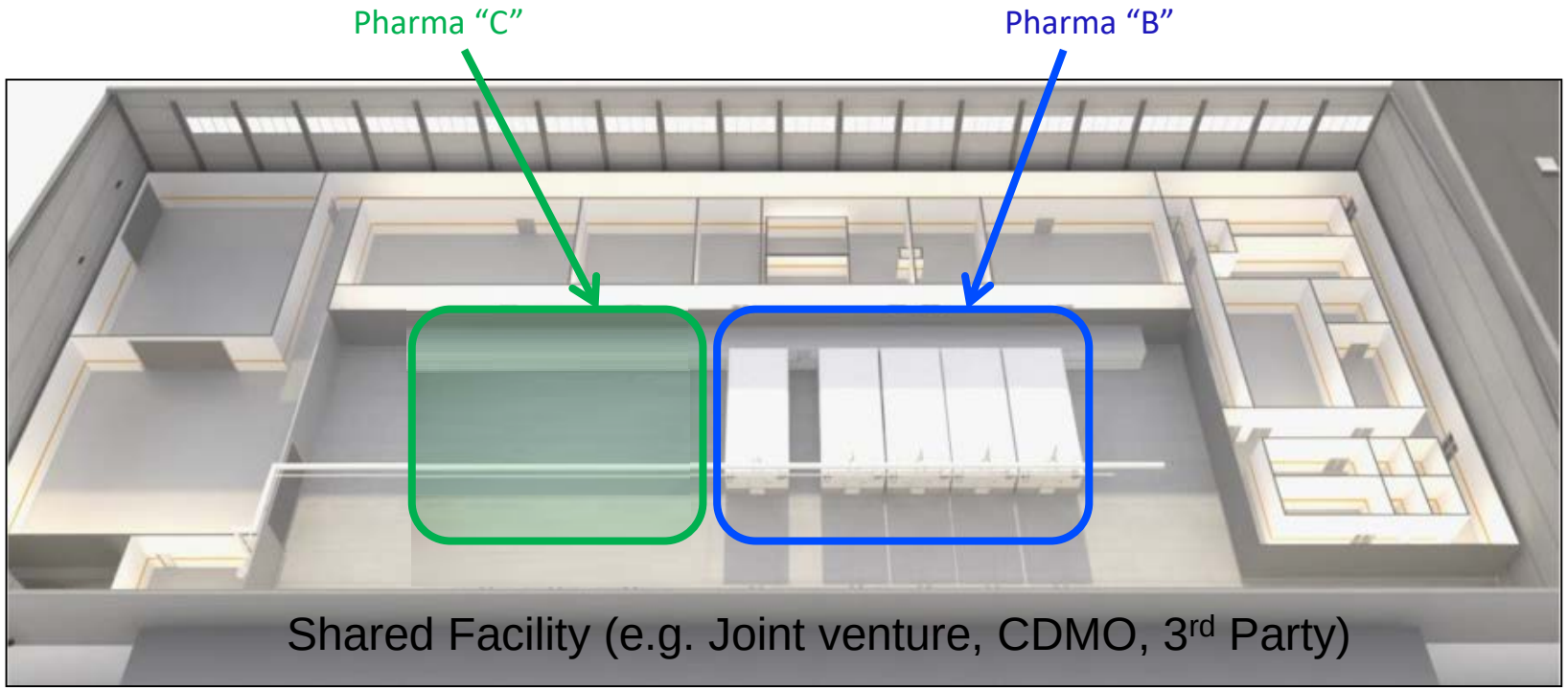
Some Emerging Opportunities – Portability (Rapid Deployment) POD Based Facility Designs

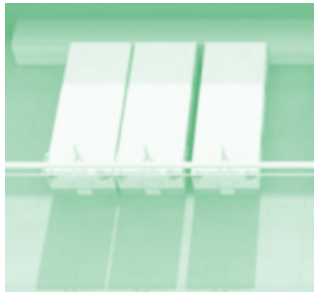
Some Emerging Opportunities – Portability (Rapid Deployment) POD Based Facility Design

Some Emerging Opportunities – Portability (Rapid Deployment) POD Based Shared Facility Designs



Some Emerging Opportunities – Portability (Rapid Deployment) POD Based Shared Facility Designs





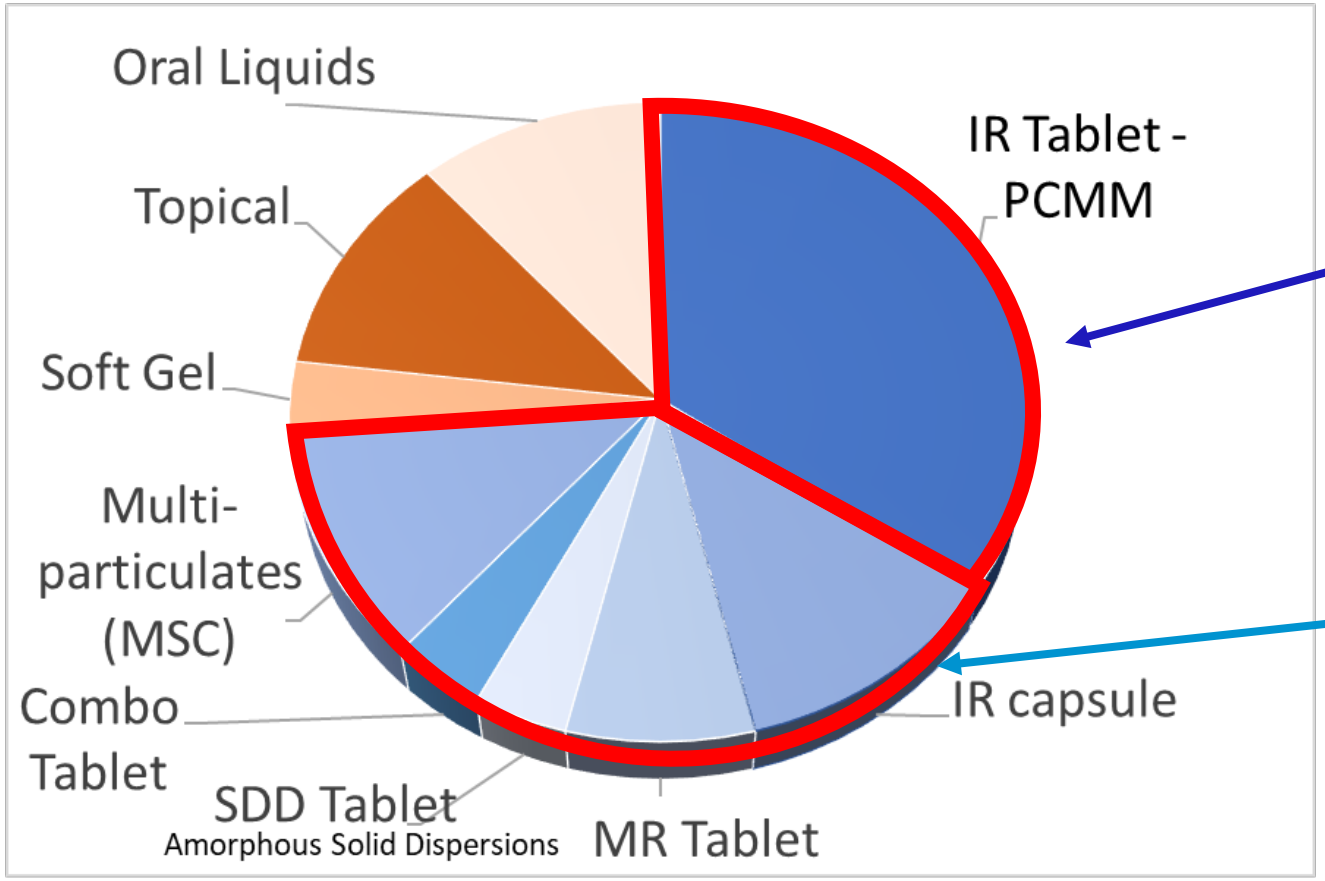
Presentation Outline

Innovation Themes for Small Molecule Solid-Oral Drug Products

- Facility and Process Innovation Drivers
- Current Landscape for Solid-Oral Drug Product
- Technology Implementation Challenges and Incremental Innovation Cycle
- Future Innovation

Pfizer Small Molecule Formulation Development

Late Stage, New Chemical Entities, by dosage form type



[Late stage (Phase IIB+) Formulations]

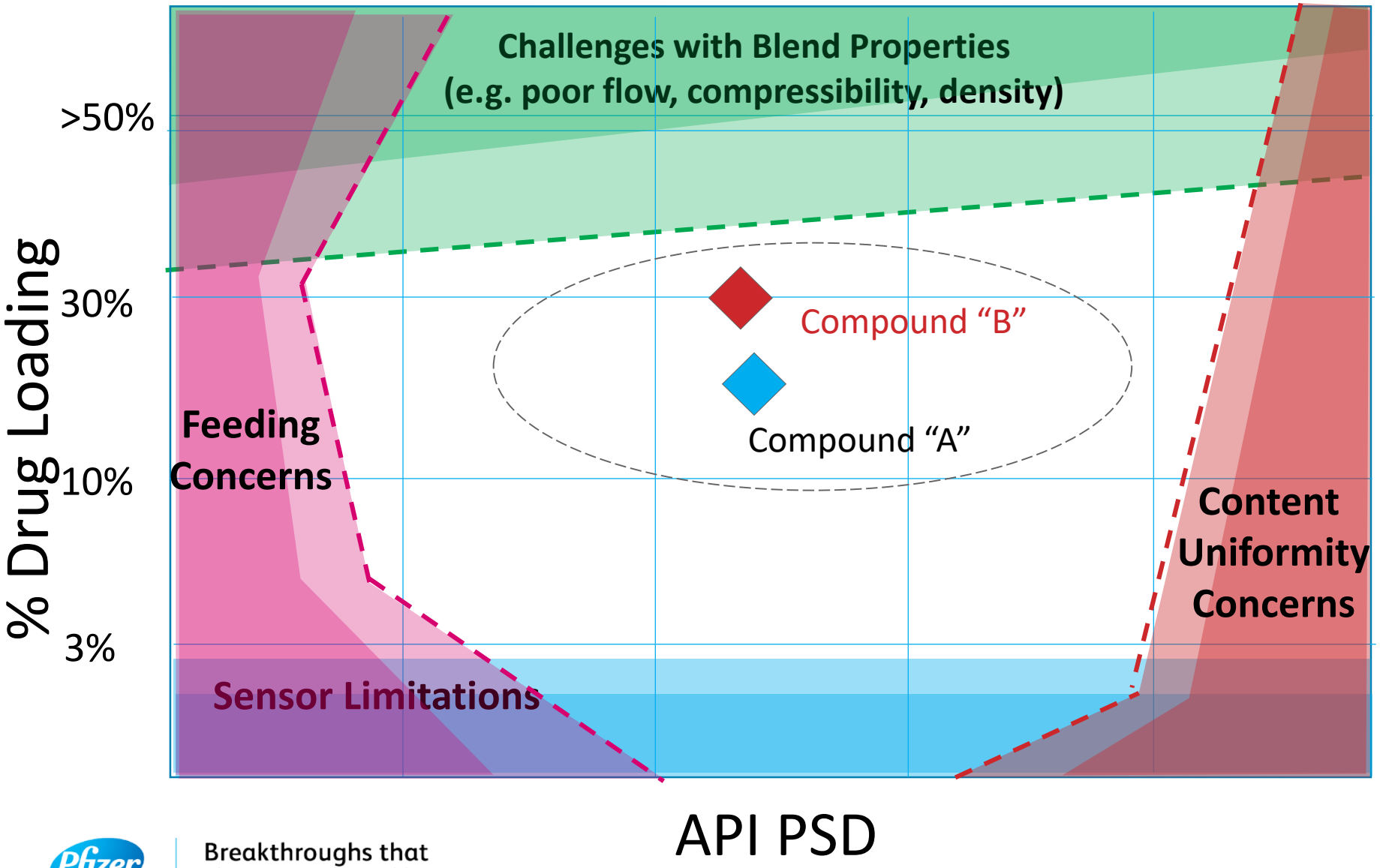
~One-third are PCMM IR Direct Compression[1]

~One-third are other Solid Oral Dosage forms

[1]as of January 2020

Applicability of Continuous DC to the broader NCE portfolio

First generation programs



Phased Adoption of Technology to NCE Portfolio

Getting off the ground: Two compound "A" and "B" selected. "Sweet spot"

Key Capital Investments (1)

R&D and Manufacturing Investments Enable Portfolio Acceleration

Groton, USA

cGMP clinical and commercial

Sandwich, England

development

Freiburg, Germany

commercial

Compound "A"
First cGMP clinical batch

Compound "A"
Inclusion into ETT program

Compound "B"
First cGMP clinical batch

Compound "A"
NDA submitted

2015 2016 2017 2018

Pfizer
Breakthroughs that change patients' lives

Key Capital Investments (2)

R&D and Manufacturing Investments Enable Portfolio Acceleration

Groton, USA

cGMP clinical and commercial

DAURISMO™

glasdegib tablets

100 mg | 25 mg

View all Press Releases

U.S. FDA APPROVES DAURISMO™ (GLASDEGIB) FOR ADULT PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKEMIA (AML) FOR WHOM INTENSIVE CHEMOTHERAPY IS NOT AN OPTION

November 21, 2018

DAURISMO is the first and only Hedgehog pathway inhibitor approved for the treatment of AML

In a randomized Phase 2 trial, DAURISMO plus low-dose chemotherapy significantly improved median overall survival in patients who were not able to receive intensive chemotherapy due to age or comorbidities – a difficult-to-treat patient population

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE:PFE) today announced that the U.S. Food and Drug Administration (FDA) approved DAURISMO™ (glasdegib), a once-daily oral medicine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy. DAURISMO is taken in combination with low-dose cytarabine (LDAC), a type of chemotherapy. DAURISMO has not been studied in patients with severe renal impairment or moderate-to-severe hepatic impairment.[1]

AML is a rapidly progressing bone marrow cancer with poor survival rates compared to people with AML is intensive chemotherapy; however, for many elderly patients conditions prior to receiving their diagnosis, intensive treatment is not ...ive treatment and face a poor prognosis.[4]

Freiburg, Germany

commercial

2018 2019

Reference

Key Capital Investments (3)

R&D and Manufacturing Investments Enable Portfolio Acceleration

Groton, USA

cGMP clinical and comme

Freiburg, Germany

commercial

Compound "B"

Inclusion into ETT program

2018

2019

Key Capital Investments (4)

R&D and Manufacturing Investments Enable Portfolio Acceleration

Powders to Film Coated Tablets* in minutes

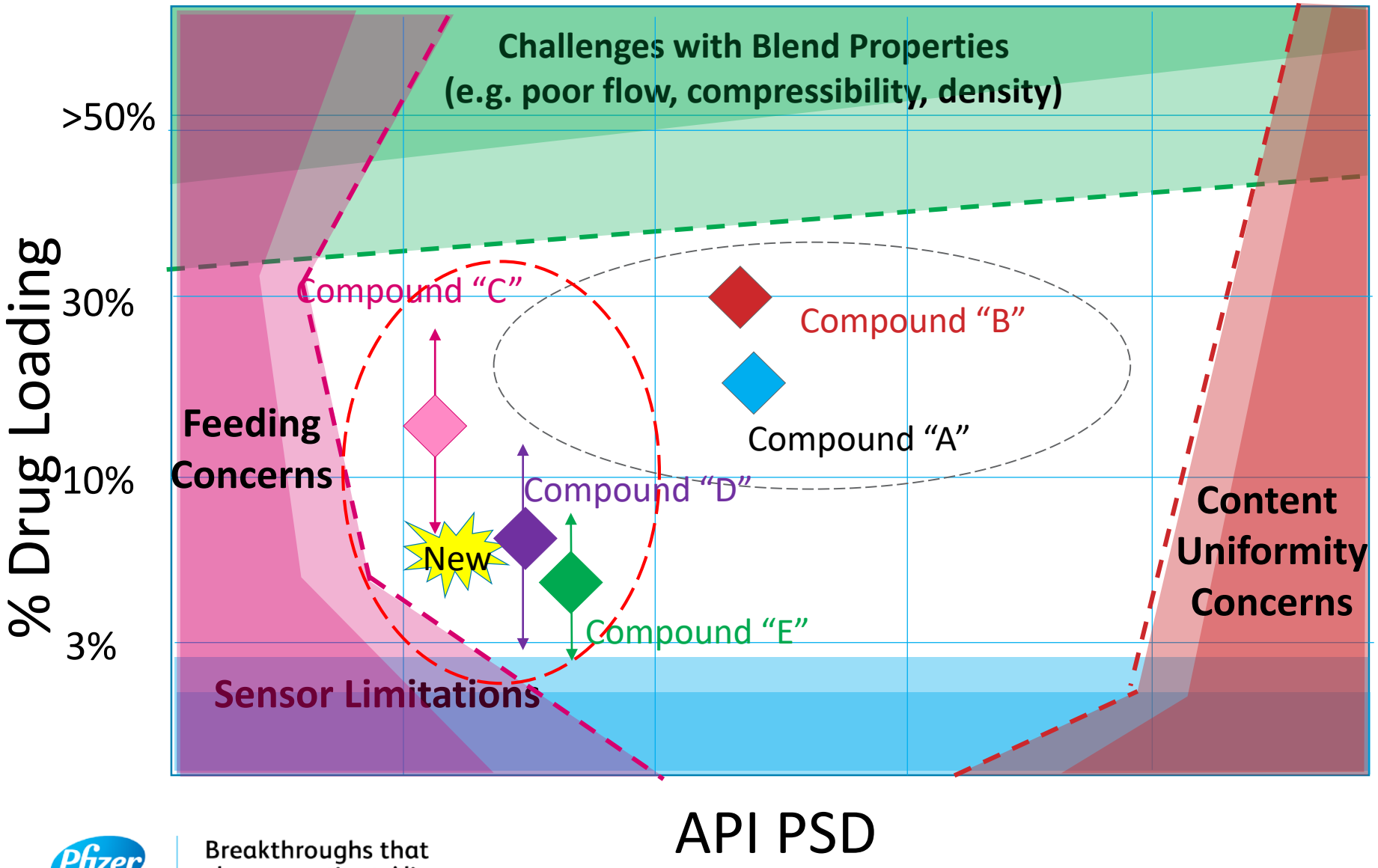
Pfizer

Breakthroughs that change patients' lives

* Continuous film-coating technology currently in development

Applicability of Continuous DC to the broader NCE portfolio

Second-wave compound.



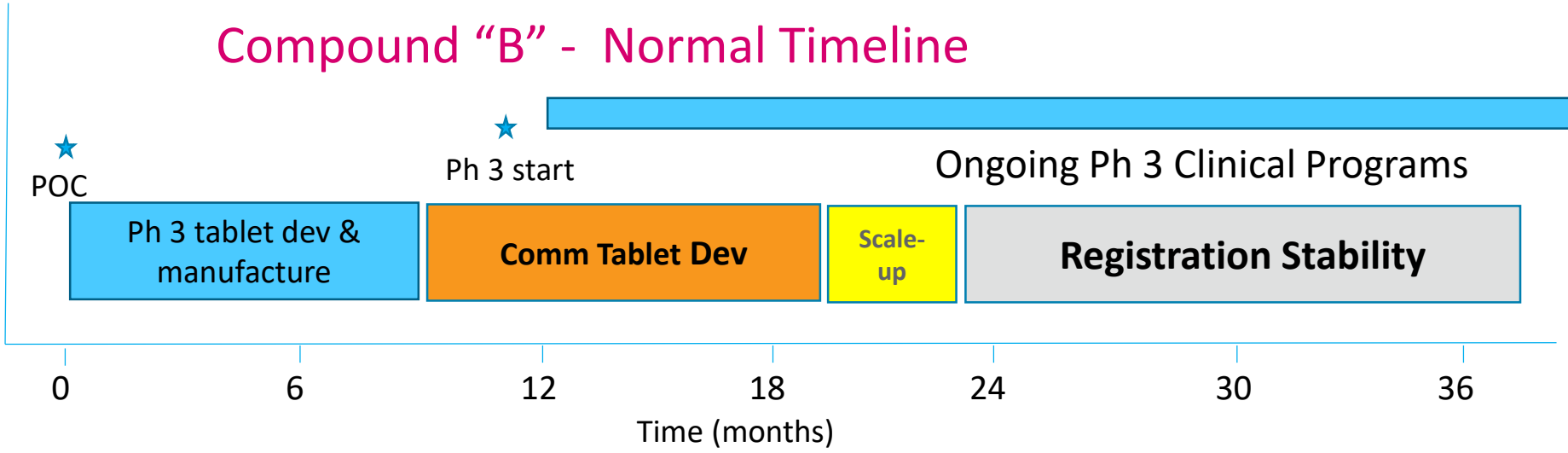
Phased Adoption of Technology to NCE Portfolio

Getting off the ground: Two compound "A" and "B" selected. "Sweet spot"

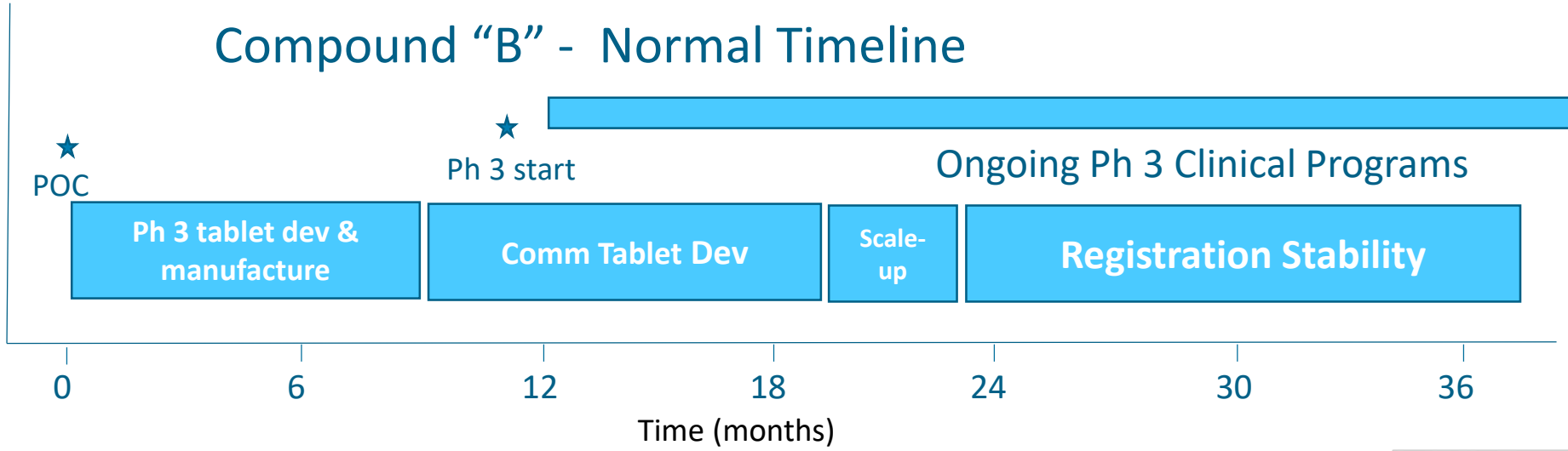
Ramp up: Compounds "C", "D", and "E"
Opportunity to probe formulation and process boundaries. Org. learning curve

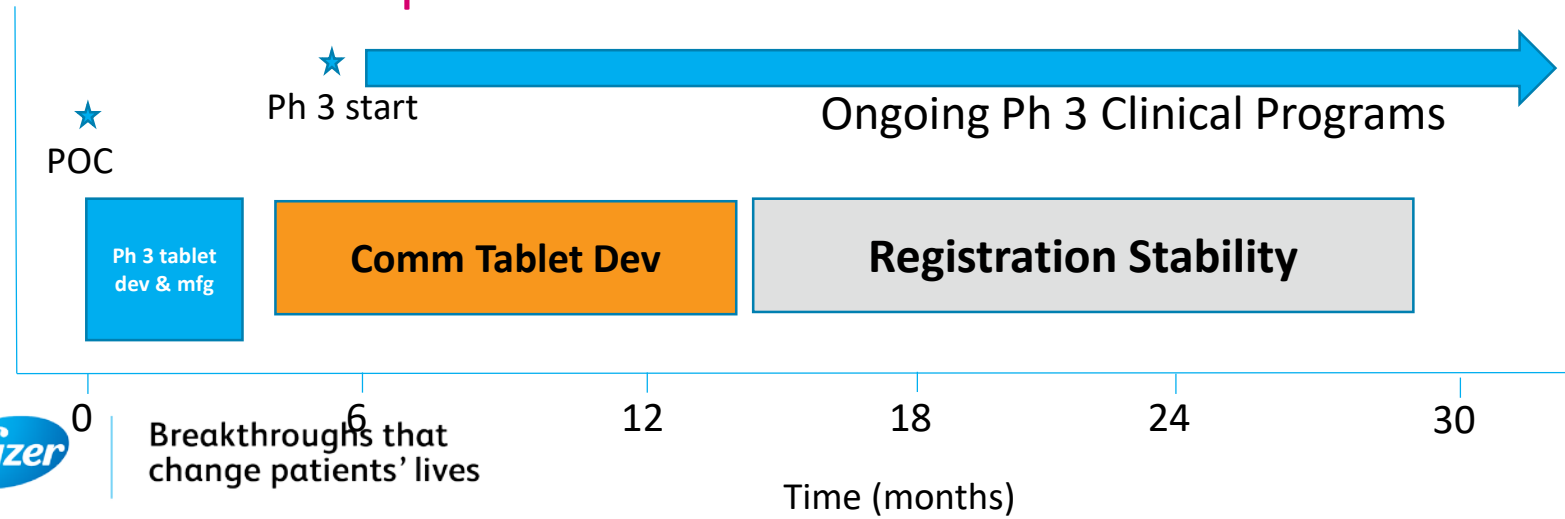
Steady state: up to 80% of solid oral IR tablets amenable to Continuous DC

Breakthrough therapies that change patients lives



Breakthrough therapies that change patients lives





PCMM accelerates:

- ✓ Ph 3 by 6 months
- ✓ Filing by at least an additional 3 months

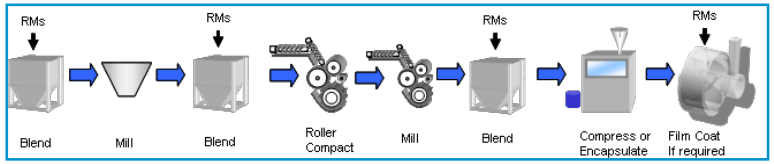
Presentation Outline

Innovation Themes for Small Molecule Solid-Oral Drug Products

- Facility and Process Innovation Drivers
- Current Landscape for Drug Product
- Technology Implementation Challenges and Incremental Innovation Cycle
- Future Innovation

PCMM Technology – Incremental Innovation

Batch Processing/
Technology Transfer Paradigm

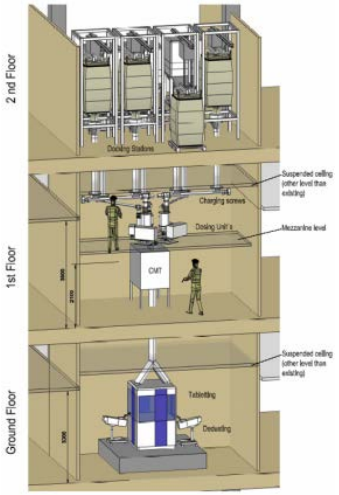


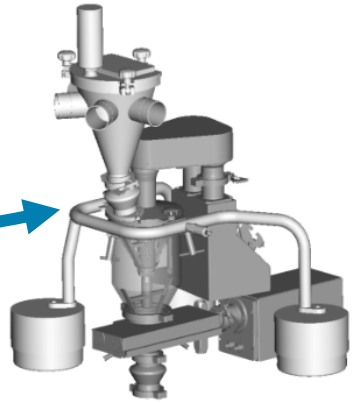
Ideation/
Prototyping/
Learning

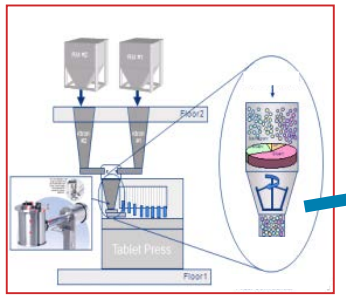
Breakthroughs that
change patients' live

A Decade of Technology Evolution

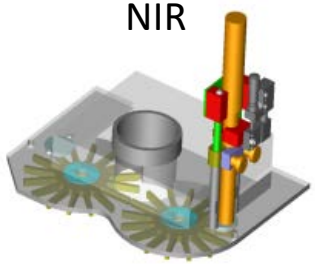
Prototyping, Iteration, Learning

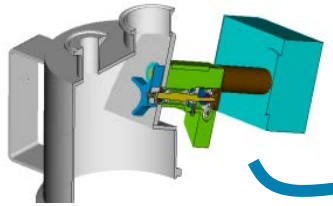




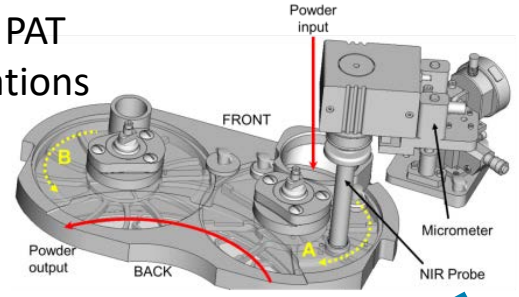


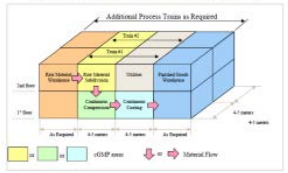
Feed Frame
NIR



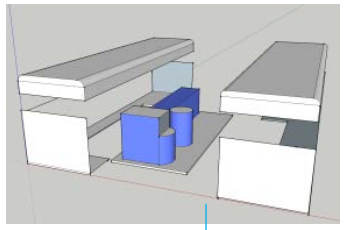


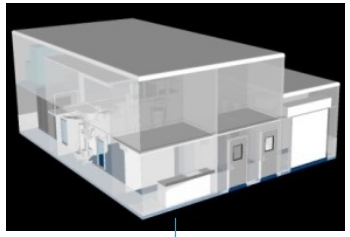
PCMM PAT
Applications





Dormant Idea





2007 2008 2009 2010 2011 2012 2013 2014

Pfizer

Breakthroughs that
change patients' lives

PCMM Technology – Incremental Innovation

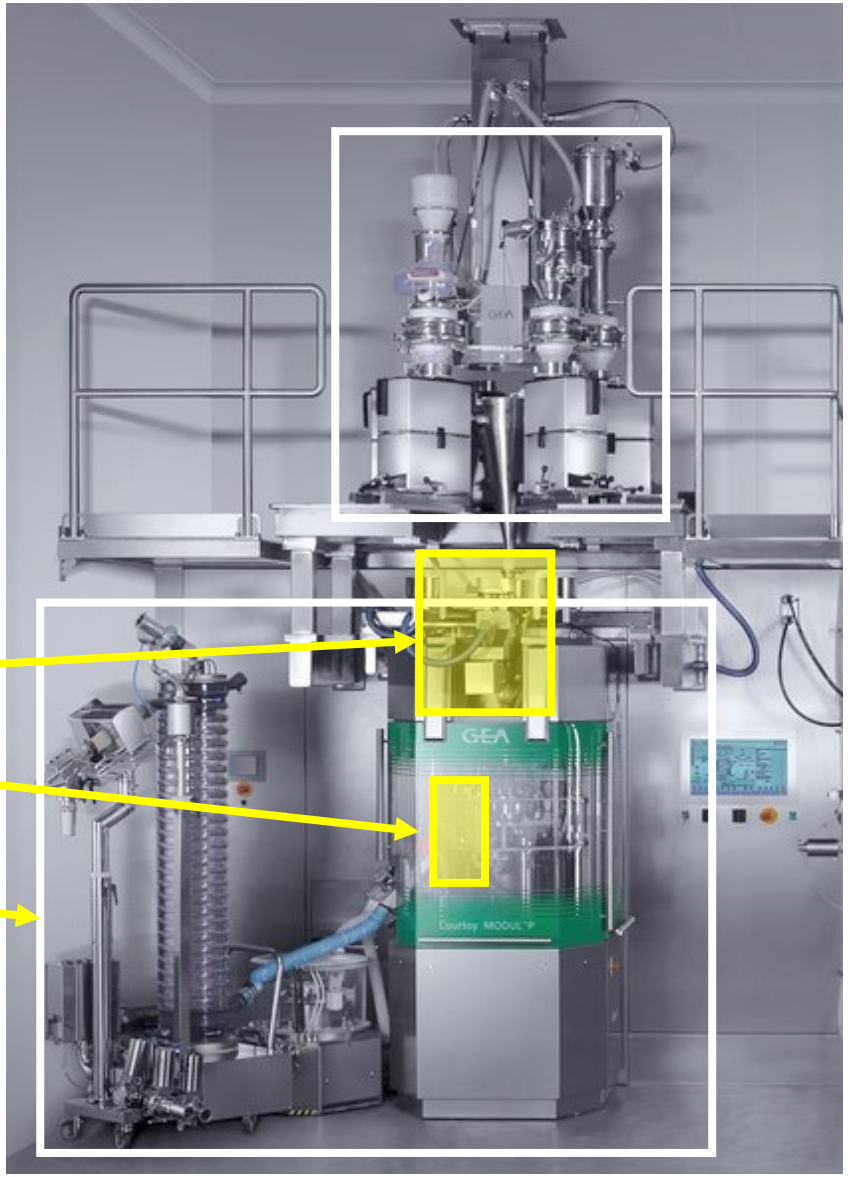
Driving Innovative and Incremental Changes

Existing Technologies

- Formulation components
- Material Transfer Systems
- Rotary Tablet Press
- Gravimetric Feeders

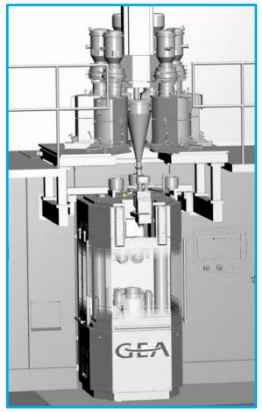
Innovative Technologies

- Vertical Powder Mixer
- NIR Feed Frame probe
- Integrated Control w Real-time decision making
- POD-based facilities

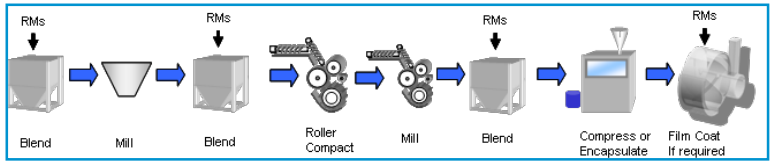


PCMM Technology – Incremental Innovation

Integrated Development
And Manufacture
Accrue Knowledge over time



Batch Processing/
Technology Transfer Paradigm



Innovation
Step Change

Ideation/
Prototyping/
Learning

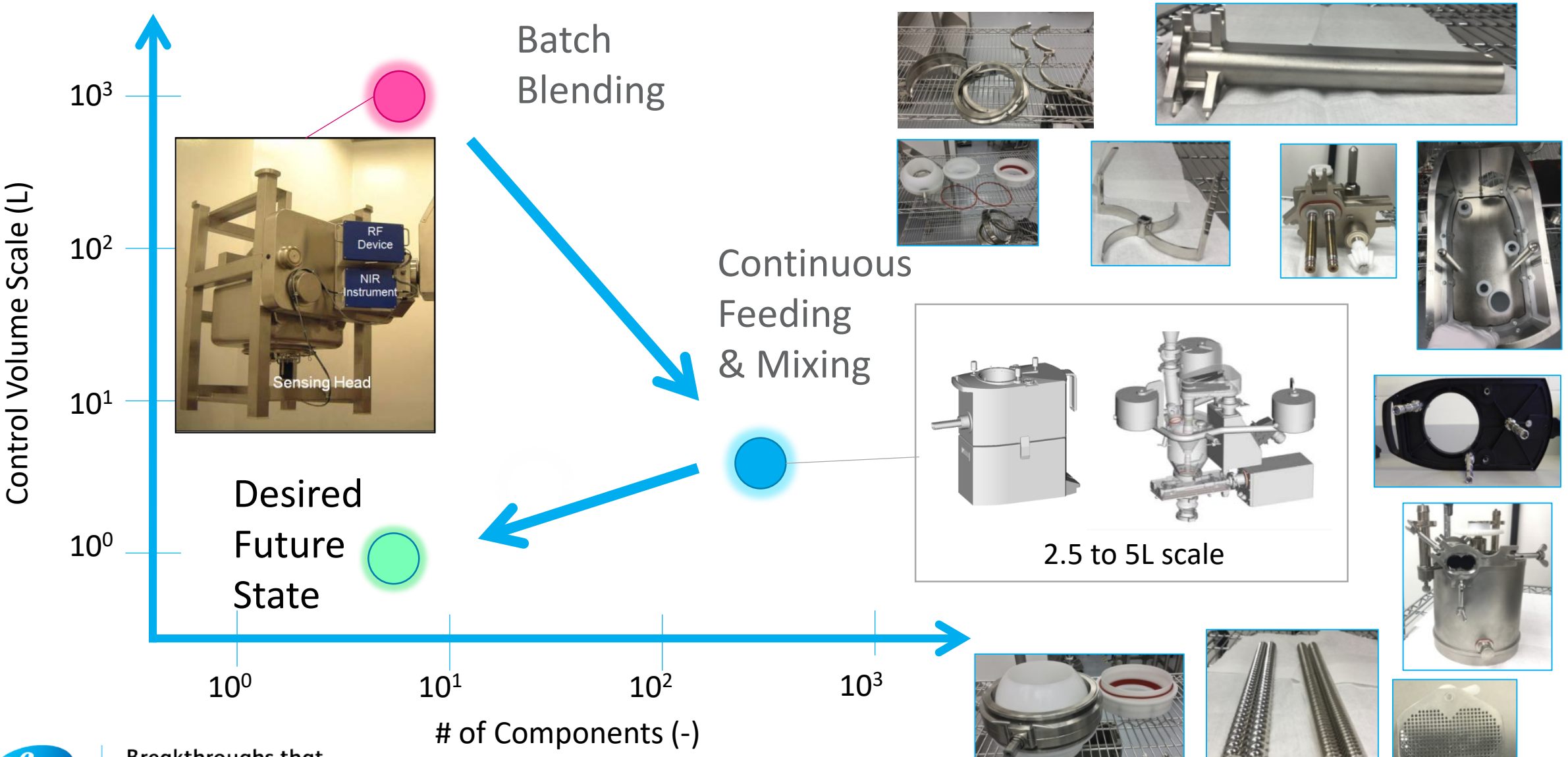
Incremental Innovation

Technology leaders supporting implementation

- Global regulatory engagement
- Completing global installations
- Prototyping adjacent technologies
- Workforce planning
- Process Efficiencies
- Change over and cleaning efficiencies

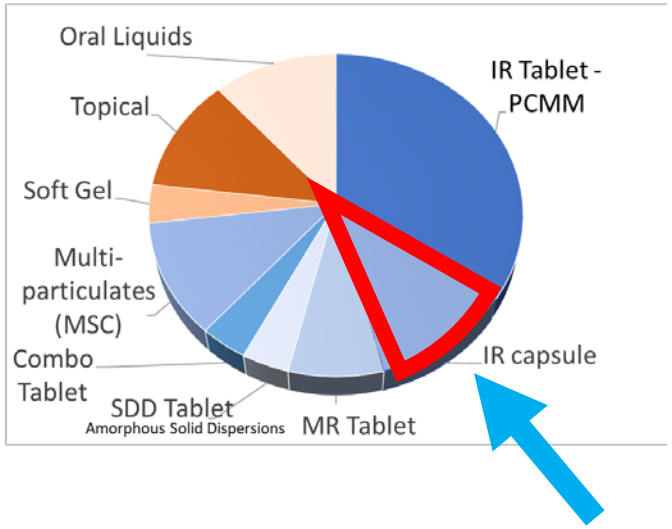
PCMM Technology Incremental Innovation (1)

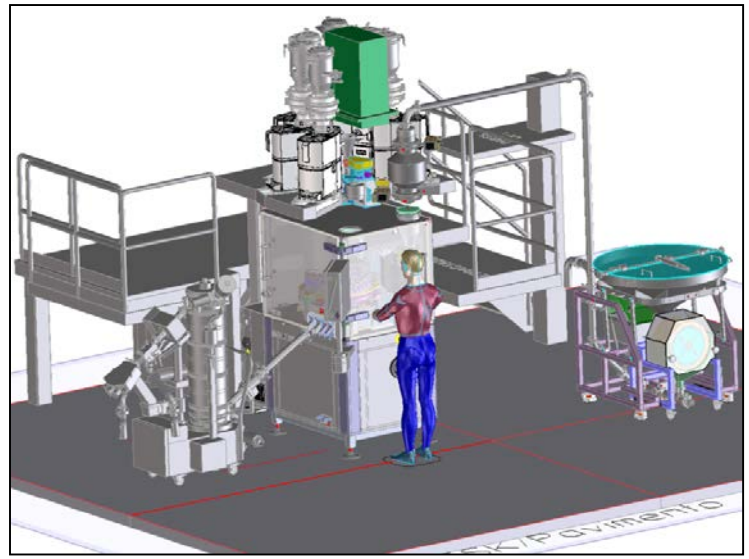
Improving Process Efficiencies - Change-over and Cleaning / Cycle Time Reduction



PCMM Technology Incremental Innovation (2)

Process Modularity – Continuous Blending→Encapsulation





Conceptual Design
Continuous Blending → Encapsulation

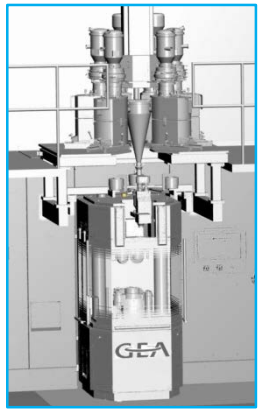
Presentation Outline

Innovation Themes for Small Molecule Solid-Oral Drug Products

- Facility and Process Innovation Drivers
- Current Landscape for Drug Product
- Technology Implementation Challenges and Incremental Innovation Cycle
- Future Innovation

Next Generation Technology Innovation

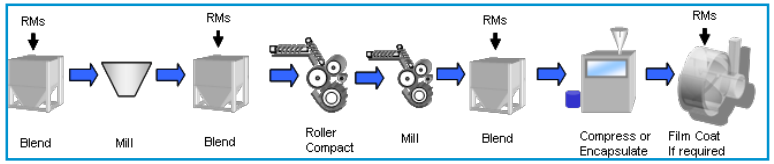
Integrated Development
And Manufacture
Accrue Knowledge over time



Next Generation Innovation

- Computational Process Modelling
- Digital Design and Big-Data
- Dose flexibility for diverse patient populations
- Pre-competitive, open Innovation

Batch Processing/
Technology Transfer Paradigm

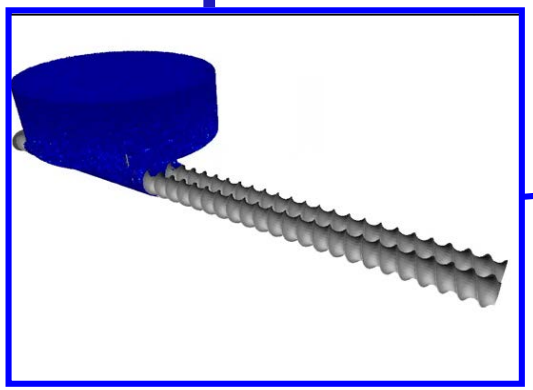


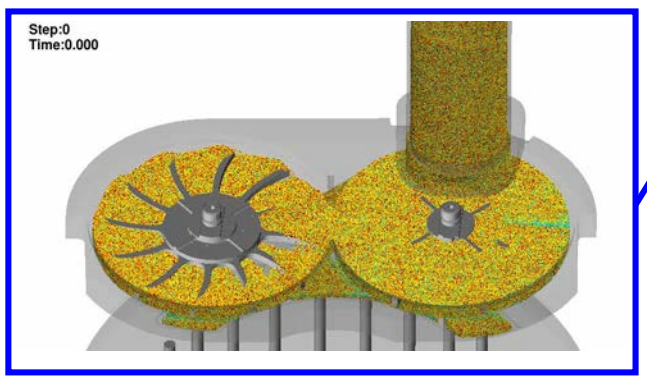
Innovation
Step Change

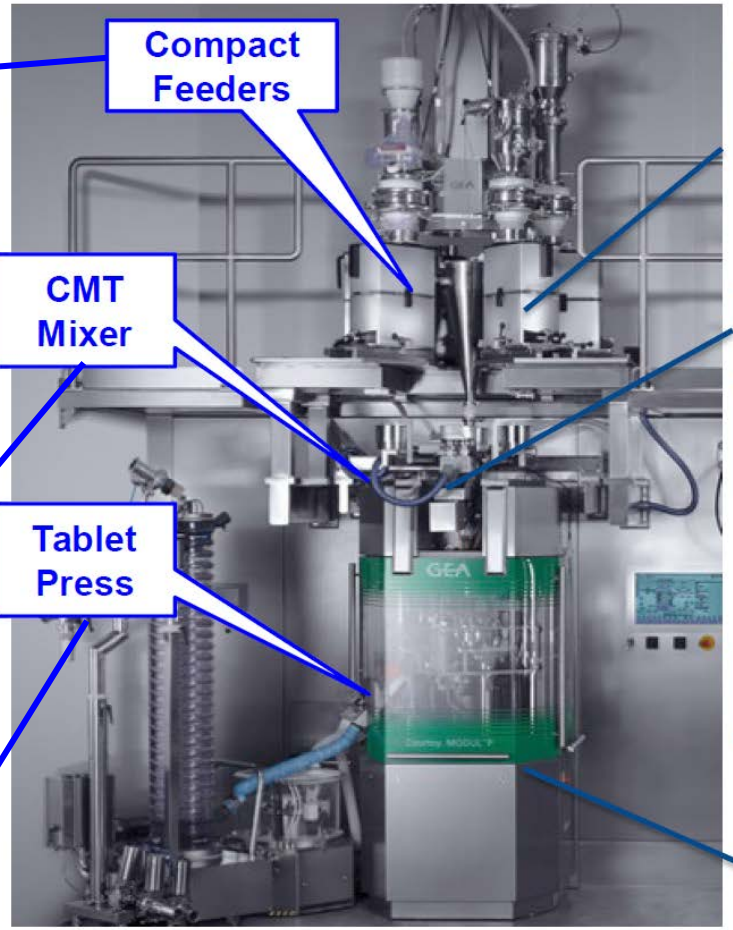
Pfizer

Breakthroughs that change patients' lives

Process Intensification Yields DEM Model of a Direct Compression Line







Compact Feeders

Minimize Feed Variability

CMT Mixer

Achieve CMT Ideal Mixing Conditions

Achieve CMT Mean Residence Time

Achieve target Extent of Lubrication

Mass Throughput (Mass in = Mass out)

Tablet Press

Achieve target Tablet Physical Properties

Pfizer | Breakthroughs that change patients' lives

research center pharmaceutica engineering

The creation of a Digital Twin for PCMM DC

Digital Twin PharmaMV – gFP allows new functionalities thanks to the connection with data of the physical system.

Sandwich development

Groton cGMP clinical & commercial

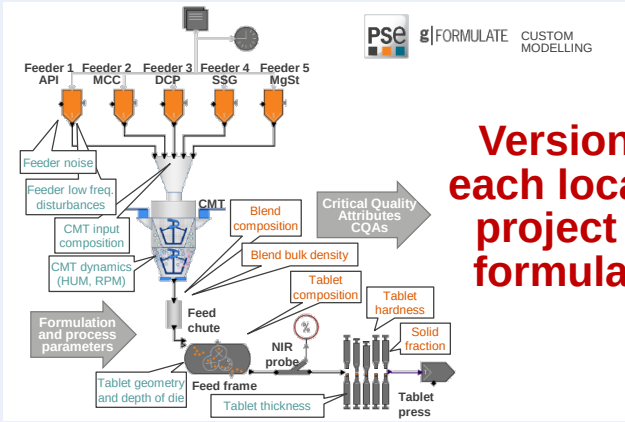
Advanced process control (APC)

Digital Design

Process control / monitoring

DIGITAL TWIN

ADDOPT



Version for each location, project and formulation

Virtual PCMM DC process

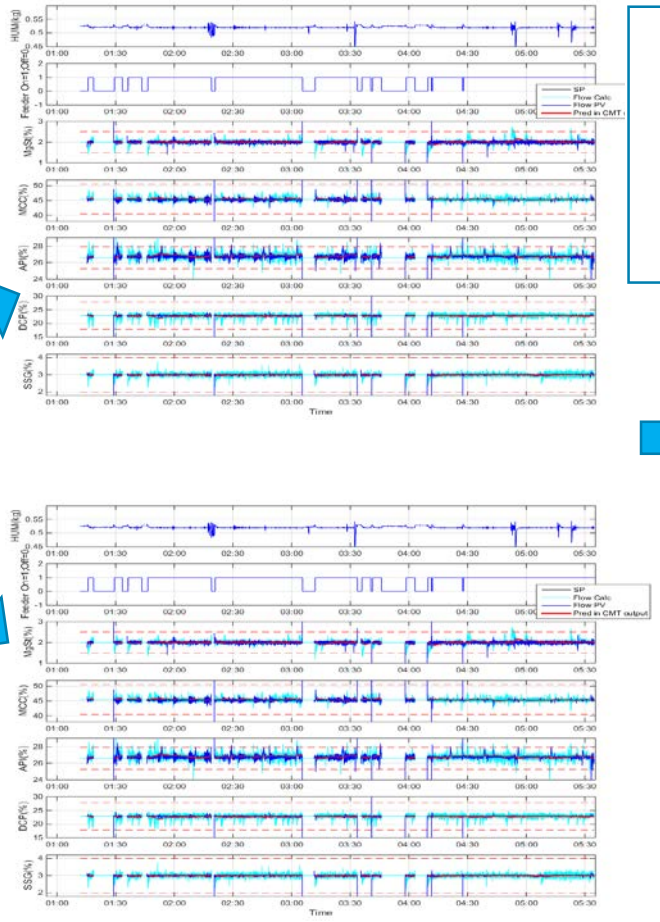
Transforming Data into Insight and Knowledge

Process Health Condition Monitoring

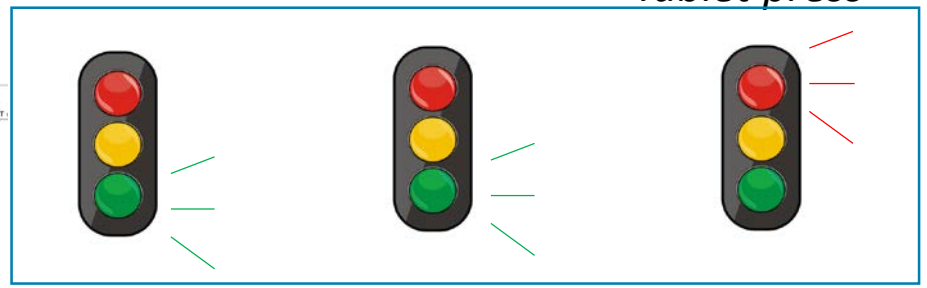
Tags

Feeder 5 Mass Flw PV
Feeder 5 Mass Flw SP
Feeder 6 Mass Flw PV
Feeder 6 Mass Flw SP
Feeder 7 Mass Flw PV
Feeder 7 Mass Flw SP
Feeder 8 Mass Flw PV
Feeder 8 Mass Flw SP
Feeder 9 Mass Flw PV
Feeder 9 Mass Flw SP
Impeller 1 Speed PV
Impeller 1 Speed SP
Impeller 2 Speed SP
Impeller 1 Torque PV
Impeller 2 Torque PV
Impeller 2 Speed PV
Exit Valve Ext CTL P
Delta EV
Exit Valve Ext CTL SP
Hold up Mass- PV
Delta HUM
Hold up Mass - SP
Displacement pre-comp
Dwell time pre-compre
Dwell time final comp
Press On/Off
Press Level Sensor
Combi Teste weight
Combi Tester Thicknes
Combi Tester Hardness
Feeder 1 Speed PV
Feeder 1 Speed SP
Feeder 2 Speed PV
Feeder 2 Speed SP
Nominal main compress
Nominal main compress
Turret Speed SP
Depth Fill PV
Displacement final co
Feeder 5 Mass Flw PV
Feeder 6 Mass Flw PV
Feeder 7 Mass Flw PV
Feeder 8 Mass Flw PV
Feeder 9 Mass Flw PV
Hold Up Mass PV
Press Level Sensor
Turret Speed SP
Turret Speed OP
Press On/Off
Fall-feeder
Fin
Fout
Delta F
Delta M
Measured Delta M
M
Exit Valve Position PV
Exit Valve Position SP
Displacement pre-compression
Displacement final compression
Dwell time pre-compression
Dwell time final compression
Press On/Off
Press Level Sensor
Wavelength 1662
Wavelength 1899
Wavelength 1666
Wavelength 1730
PLS Prediction
Exit Valve Position PV
Exit Valve Position SP

Real-time process trending



Feeder *CMT* *Feed-Frame/ Tablet press*



Latent Variable Model (ONLINE) e.g.: PCA/PCR

- Simple process health indicators
- Diagnostic information in the event when a fault occurs


Statistical process monitoring: basics and beyond

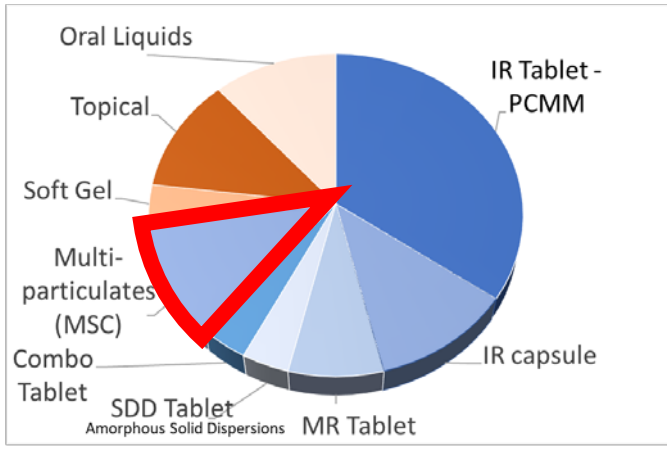

Multivariate process and quality monitoring applied to an electrolysis process
Part II. Multivariate time-series analysis of lagged latent variables


Process analysis, monitoring and diagnosis, using multivariate projection methods

Pfizer | Breakthroughs that change patients' lives

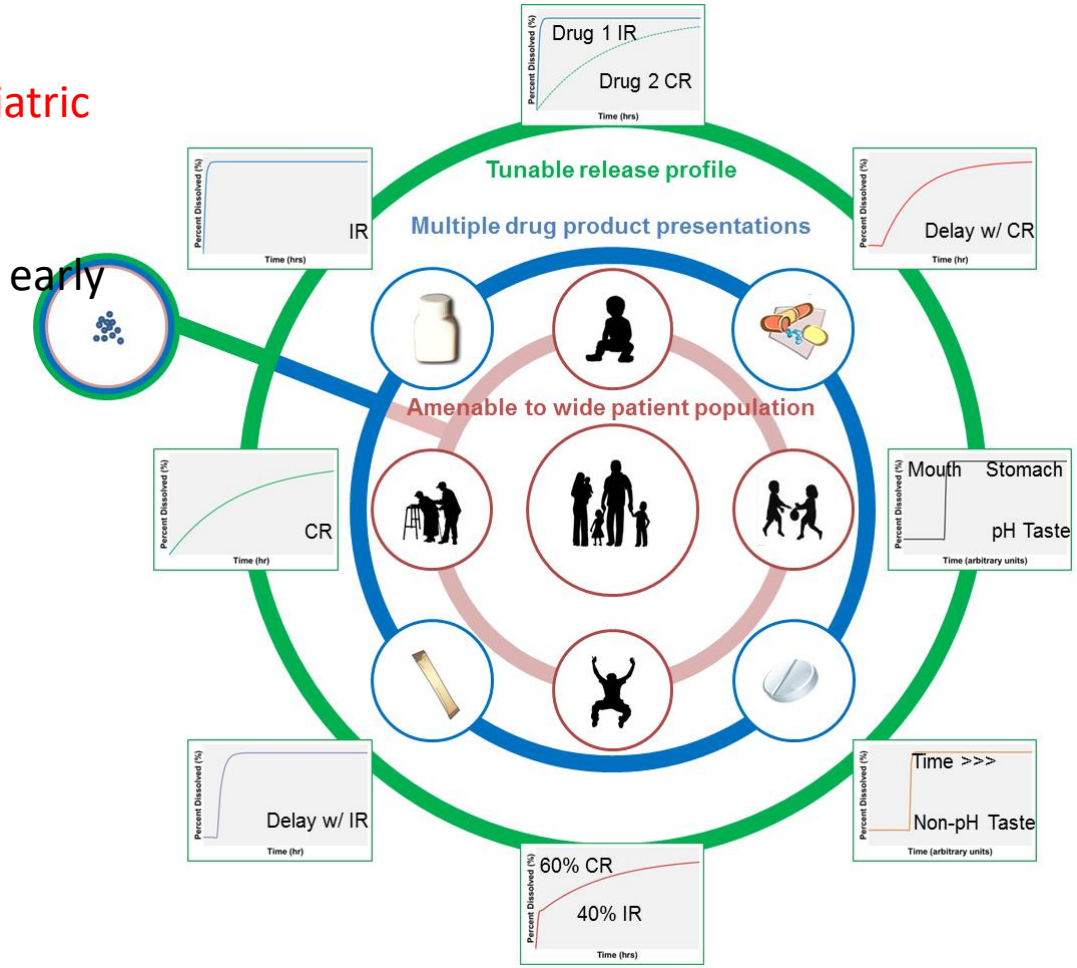
Slide courtesy of G. Cogoni

Multiparticulates Dosage Form– beyond pediatrics



Drug Development Versatility

- Can be used for both adult and pediatric patients
- Flexibility in dose options
- Acceleration of programs that show early signs of efficacy
- Rapid translation from Phase I to Commercial



Drug Delivery Versatility

- Taste Masking
- Pulsatile
- Enteric (regional targeting)
- Controlled Release
- Immediate Release
- Multi-drug combination
- Multi-release profile combo

Overview of pediatric multiparticulate platform manufacturing flow train

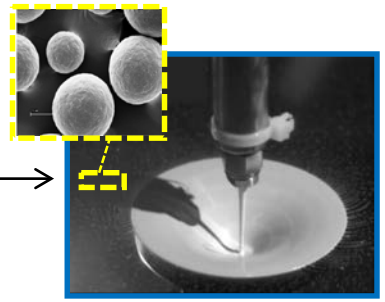
AP

Blending / Delumping

Powder Feed / Melt & Convey

K-tron feeder; twin screw extruder

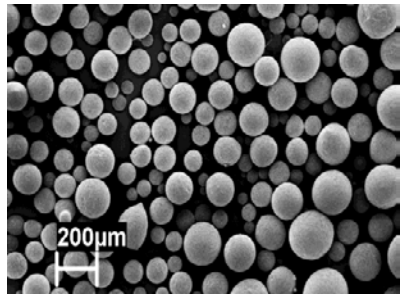
Melt Spray Congeal (MSC) production



Spinning Disk Atomization

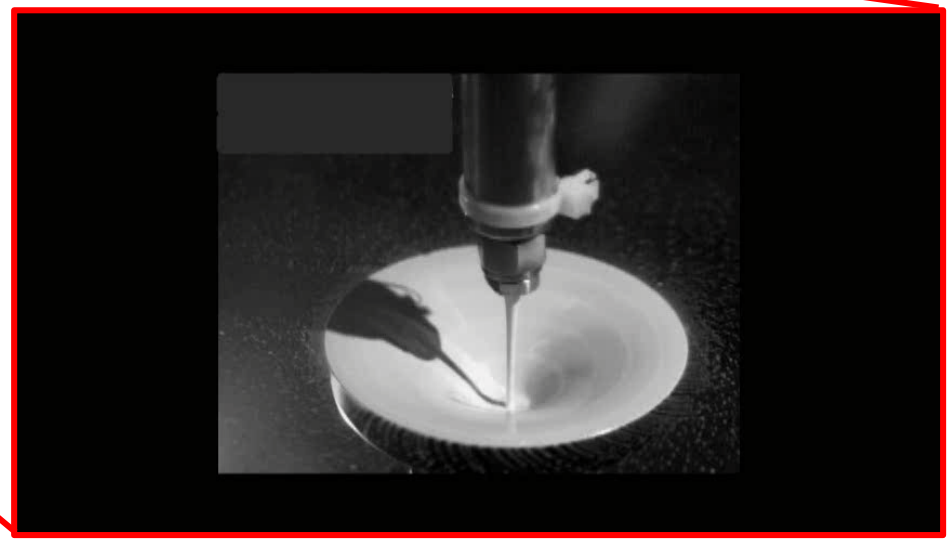
Sieving

Freund Turbo Screener



Additional post-processing steps

Continuous processing

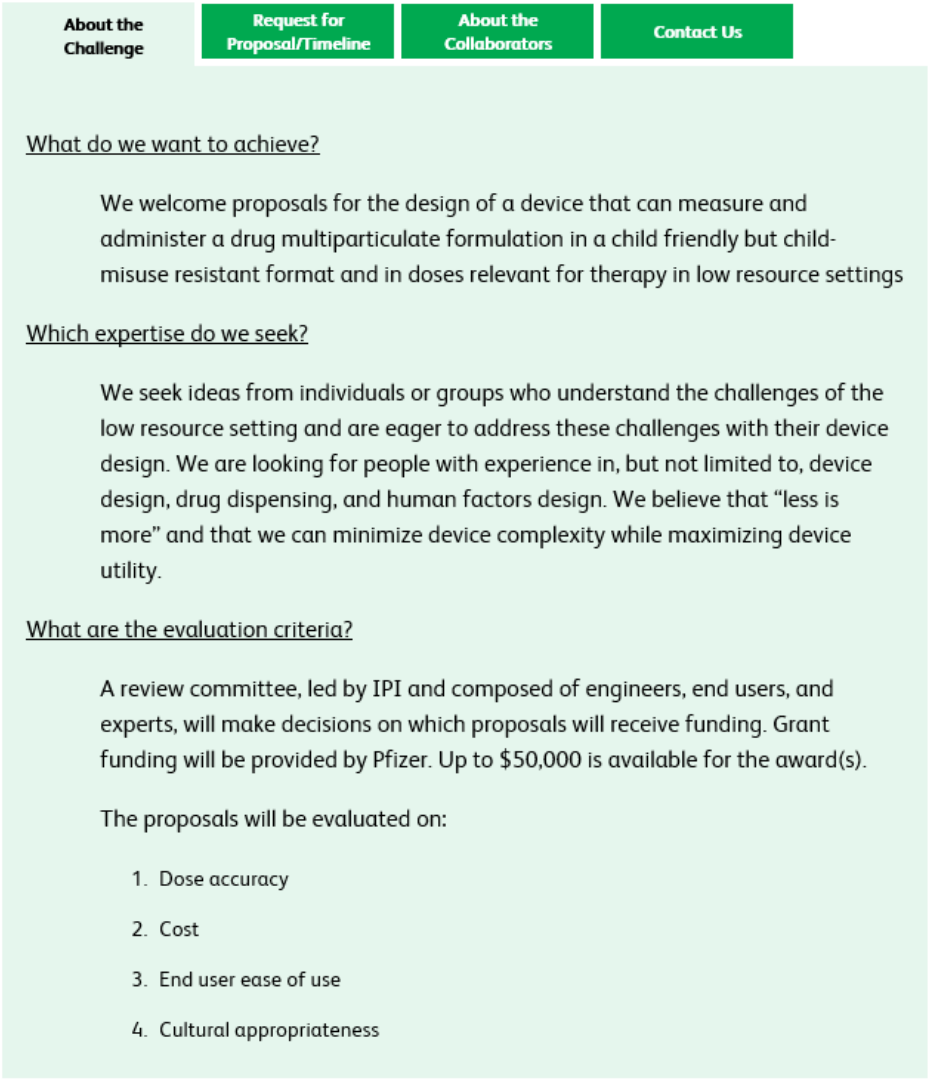


Slides courtesy of J. Bartlett

Institute of Pediatric Innovation and Pfizer collaborate on open innovation pediatric device challenge - 2016

System for Dosing and Dispensing Multiparticulate Formulations of Pediatric Drugs - Request for Proposals

- The Institute of Pediatric Innovation (IPI) and Pfizer collaborated on an open innovation global grand challenge
- Seek innovative ideas for a **system consisting of a package and dispensing device** that will be used to **deliver oral solid multiparticulate** (MP) medicines to children.
  - Measure and Administer
  - Child Friendly, but misuse resistant
  - Economical – intended for developing nations
- **Parties entering** the competition including the winning entity will **retain ownership of related intellectual property**
- The organization who submits the winning design will be **awarded a $50K seed grant** to fund 'proof of concept' steps toward development of the device



About the Challenge | Request for Proposal/Timeline | About the Collaborators | Contact Us

What do we want to achieve?

We welcome proposals for the design of a device that can measure and administer a drug multiparticulate formulation in a child friendly but child-misuse resistant format and in doses relevant for therapy in low resource settings

Which expertise do we seek?

We seek ideas from individuals or groups who understand the challenges of the low resource setting and are eager to address these challenges with their device design. We are looking for people with experience in, but not limited to, device design, drug dispensing, and human factors design. We believe that "less is more" and that we can minimize device complexity while maximizing device utility.

What are the evaluation criteria?

A review committee, led by IPI and composed of engineers, end users, and experts, will make decisions on which proposals will receive funding. Grant funding will be provided by Pfizer. Up to $50,000 is available for the award(s).

The proposals will be evaluated on:

1. Dose accuracy
2. Cost
3. End user ease of use
4. Cultural appropriateness

Slides courtesy of J. Bartlett

Public Press Release of the winners from the grand challenge announced Dec 15, 2016

- Two companies (two different devices) were chosen as winners
  - **HS Design and Rochling**
  - **Balda a Stevanato Group Brand**
- Seed Grants were awarded of $50,000 to each winner

Pediatric Open Innovation Challenge Grantees Awarded $50,000 by the Institute for Pediatric Innovation and Pfizer

The Institute for Pediatric Innovation (IPI) and Pfizer have partnered to award two $50,000 grants to medical companies for the development of a device to dispense potentially life-saving medicines for children in low-resource settings. Pfizer has developed a new formulation for pediatric drug administration, and together with IPI held a challenge for companies from around the country to design a dispensing device for pediatric drug formulation.

IPI/Pfizer Public Press Release Dec 15,2016 http://www.prweb.com/releases/2016/12/prweb13

Final Comments

- Technology innovation is transforming development approaches for Pfizer NCE portfolio of compounds
  - Up to ~70-80% of IR solid, oral portfolio anticipated to utilize PCMM platform technology
  - For some programs, technology investments are opening opportunities for speed to markets/patients
  - Regulatory engagement continues worldwide
- Challenges are emerging …. Internal technology innovators are balancing
  - Implementation needs ←→ Incremental innovation ←→Next Gen innovation
- Organizational learnings from first generation technology innovation are paving the way for the adoption of tomorrow's technologies

Acknowledgments

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

- Especially
  - J. Bartlett
  - P. Doshi
  - G. Cogoni
  - P. Nixon