

# **PROSPECTS & CHALLENGES FOR PSE IN HEALTHCARE**

2040 Visions of Process Systems Engineering  
*Symposium in Honor of Retirement of  
Professor George Stephanopoulos*

**G V Rex Reklaitis**

June 1-2, 2017

# OUTLINE

- Current Context
- Challenges for 2040
  - Process & Product Design
  - Advanced Manufacturing
  - Product Pipeline Management
  - Personalized /Individualized Medicine
- Summary

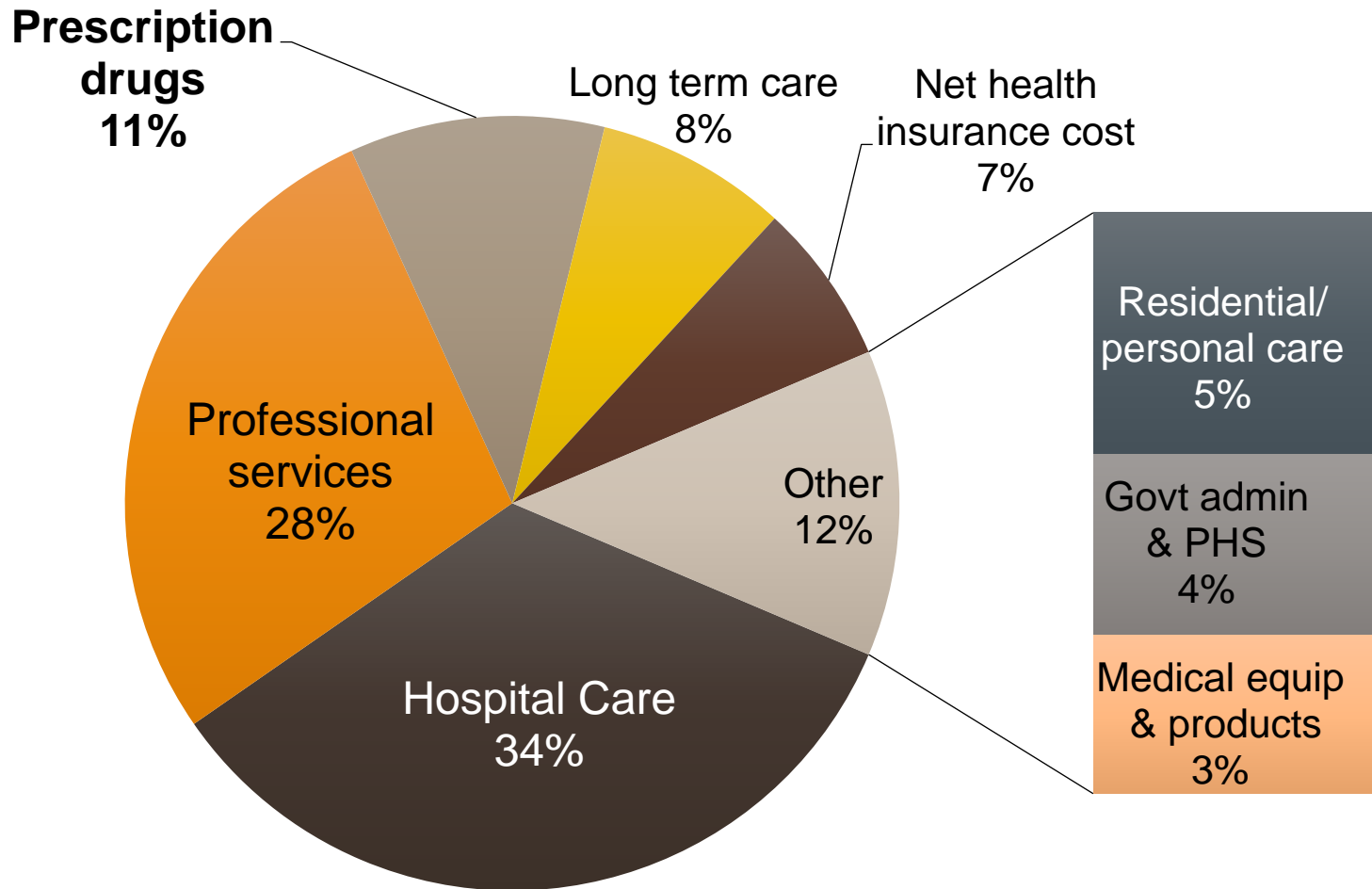
# HEALTHCARE ECONOMIC IMPACT

- Worldwide healthcare costs (2015)
  - \$7.7 trillion
  - 10% of World GDP
- US healthcare costs
  - \$3.2 trillion
  - 18% of US GDP



Keehan et al, *Health Affairs* 36, 553-563 (2017)

## 2016 National Health Expenditures



Total: \$3200 B

# PHARMA INDUSTRY CONTEXT

- \$1+ T/y Business with global supply chain
- Changing market
  - Slow growth in (ex-US) developed world
  - US growth in specialty and generic products
  - Largest Growth in countries with developing middle class (e.g., India, China, Turkey, Brazil)
  - Rest of developing world: focus on prevention & treatment of acute conditions
- R&D High Risk / High Payoff
- Highly regulated over product life cycle
- Increasingly price controlled
- Cost & quality of manufacturing emerging as significant components
  - *COGS 25+% innovators; 50+% generics*
  - *McKinsey claims could be reduced 50%*
- Increasing capacity & capability outsourcing



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

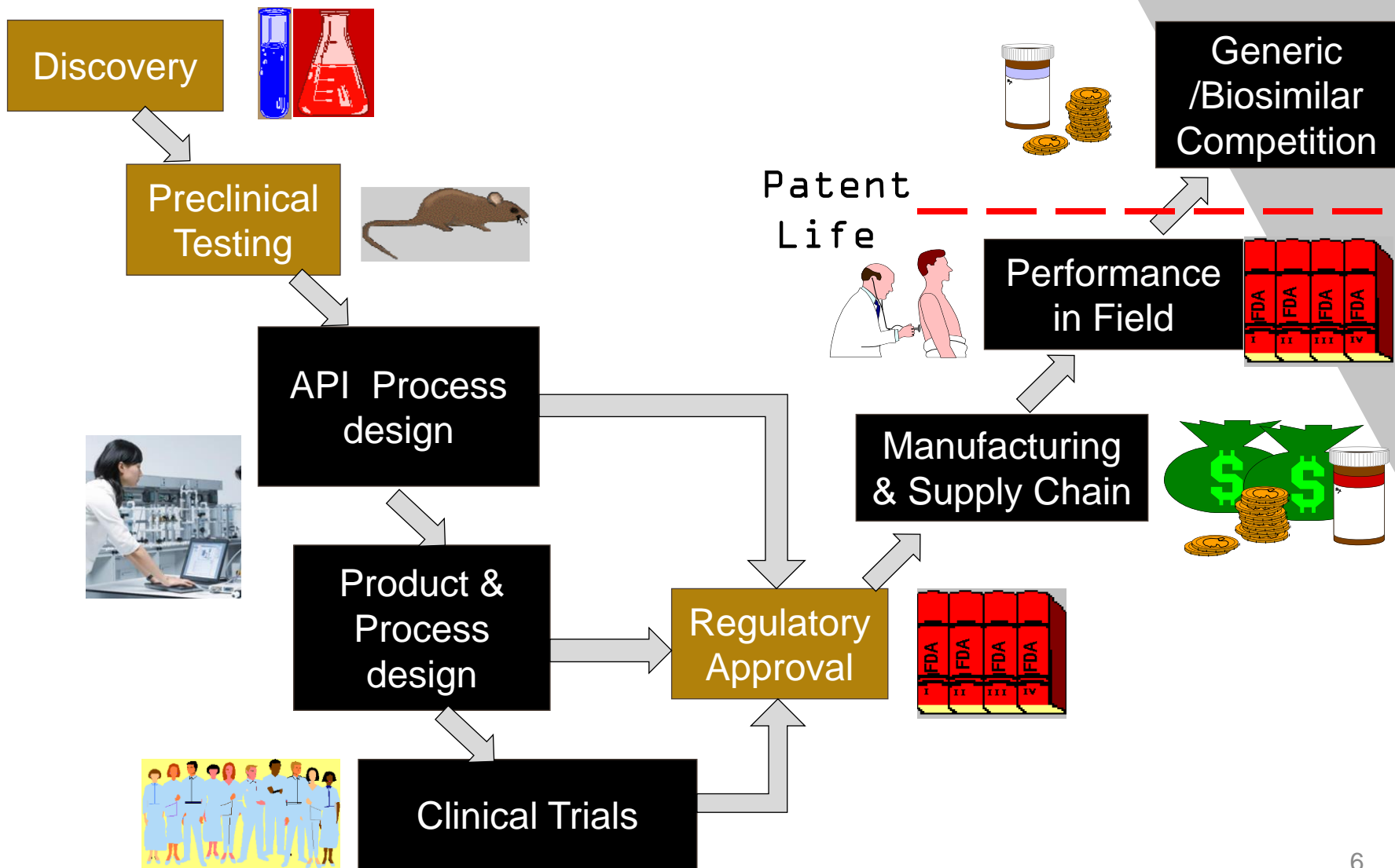


**U.S. FOOD & DRUG**  
ADMINISTRATION



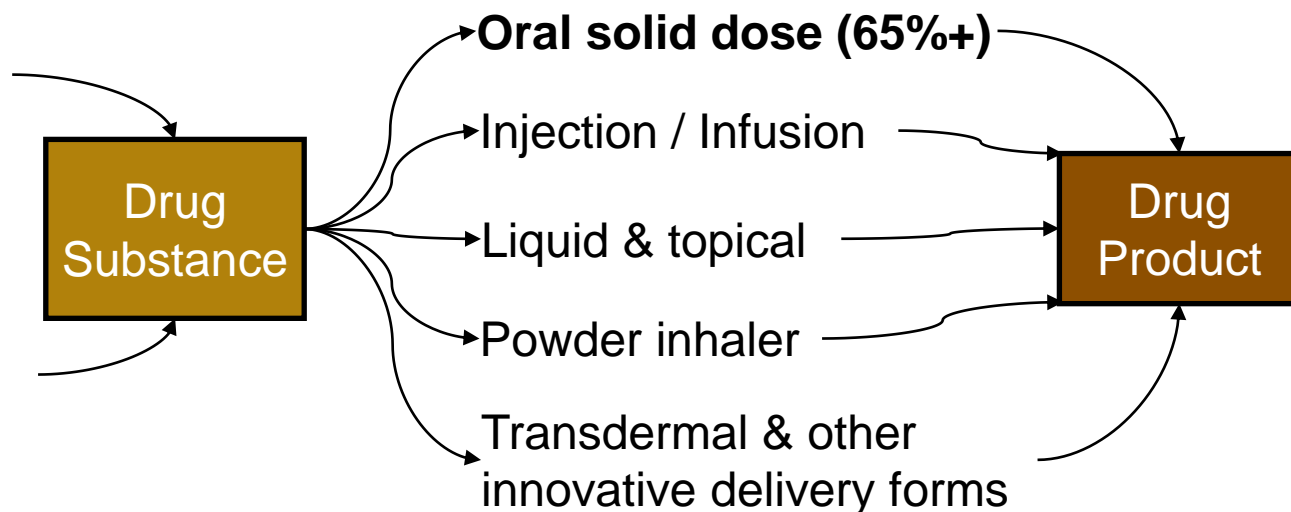
独立行政法人 医薬品医療機器総合機構  
Pharmaceuticals and Medical Devices Agency

# LIFE CYCLE OF NEW PHARMACEUTICAL PRODUCT



**Synthetic organics  
(small molecule)**

**Biologics  
(large molecule)**



**Dominance of Batch Manufacturing Mode**

- **Goal:** *Industry-wide use of knowledge- & model-based tools for process synthesis*
- **Barriers**
  - Complexity of API reaction pathways
  - Identification & minimization of impurities
  - Estimation of physical properties
- **Strengths**
  - Industry-wide recognition of benefits of models
  - Development groups now infiltrated by ChE's
  - Extensive chemical reaction databases
  - Pioneering work by Stephanopoulos group



## ***Computer-Aided Design Framework for Batch Process Development Using Hierarchical Process Synthesis***

### Route Planning

- Reaction Pathway Evaluation
- Input/Output structure,
- Preliminary Economics

Stephanopoulos, Johnson, Lakshmanan, Mavrovouniotis, Siletti, "Design-Kit", *Comp Chem Engr*, 11, 655-674 (1987)

### Stage Refinement

- BDK operation based language

### Facility Allocation

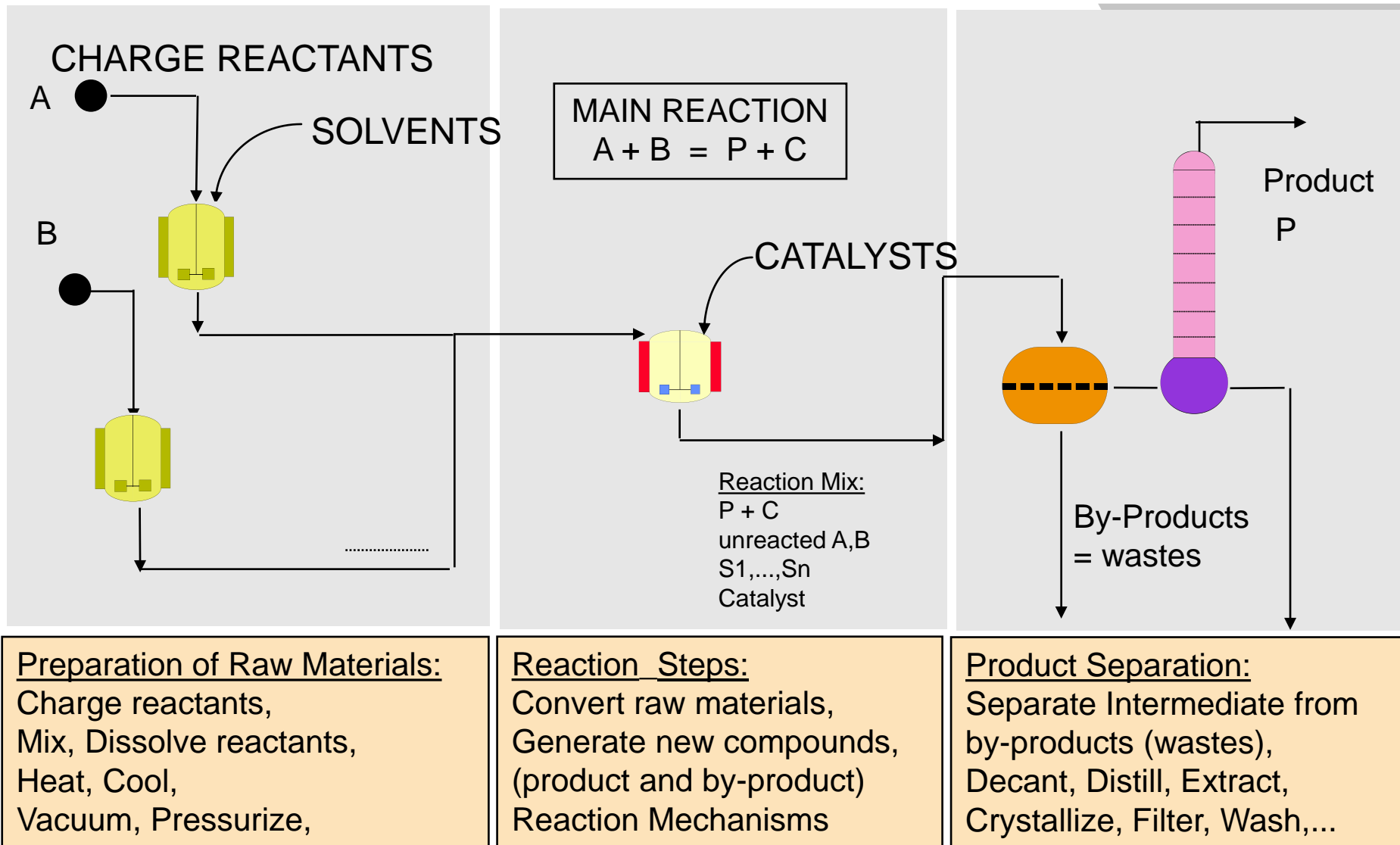
- Class Hierarchy of Equipment & Production Sites
- Minimization of Rental Costs

### Process Analysis

- Solvent Assessment
- Waste Treatment

Stephanopoulos, Ali, Linninger, Salomone, *AIChE Symposium Series* No. 323, Vol 26 2000 (FOCAPD'99)

# STRUCTURE OF BATCH PROCESSES



# INVESTIGATING A NEW STAGE

## Operation-based Language

Raw Material Preparation  
Reactions  
Separation

**Operation: EXTRACT**

EXTRACT in

Over  minutes

Using data

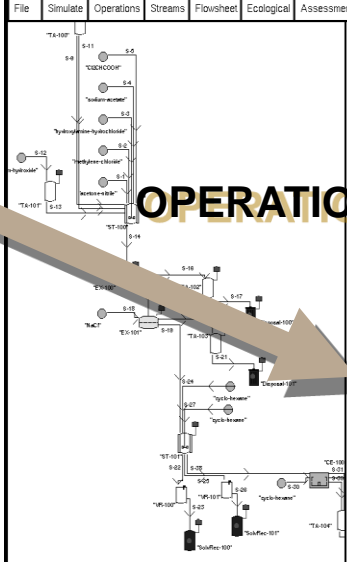
Sending bottom layer to

Giving the name

With condenser outlet temperature  degrees C

Operation Dialog

**OPERATIONS**



- BEGIN PARALLEL OPERATIONS
- BEGIN SEQUENTIAL OPERATIONS
- NOTE: acetone-nitrile is sieve dried
- CHARGE ST-100 with 44.4 kg of acetone-nitrile, with condenser outlet temperature 20 degrees C
- NOTE: Methylene-chloride is sieve-dried
- CHARGE ST-100 with 187.8 kg of methylene-chloride, with condenser outlet temperature 20 degrees C
- CHARGE ST-100 with 29.5 kg of hydroxylamine-hydrochloride, with condenser outlet temperature 20 degrees C
- NOTE: Sodium acetate must be anhydrous
- CHARGE ST-100 with 34.7 kg of sodium-acetate, with condenser outlet temperature 20 degrees C

Flowsheet      Batch Sheet

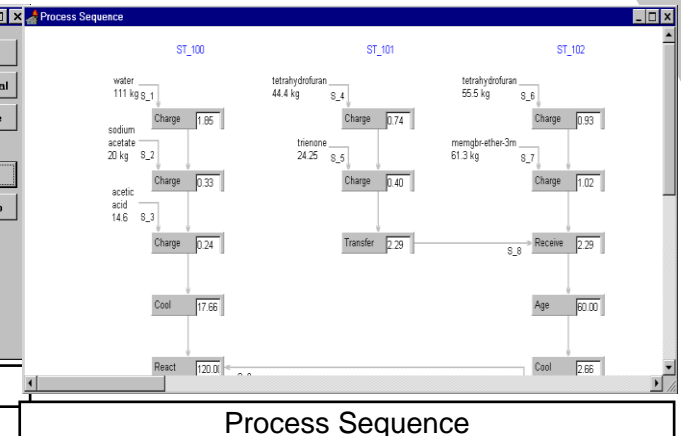
## Process Views

BatchSheet  
FlowSheet  
ProcessSequence  
StreamTable

Process Sequence

	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_10	S_11
Storage	Storage	Storage	Storage	Storage	Storage	Storage	Storage	Storage	Storage
ST_100	ST_101	ST_101	ST_102	ST_102	ST_102	ST_102	ST_100	ST_102	ST_102
14.600	44.400	24.250	55.500	61.300	68.623	185.349	44.400	44.400	44.400
0.014	0.050	0.002	0.063	0.053	0.053	0.165	0.050	0.050	0.050
1.042	0.880	11.330	0.880	1.157	1.306	1.121	0.880	0.880	0.880
25.000	25.000	25.000	25.000	25.000	25.000	12.500	25.000	25.000	25.000
1.000	1.000	1.000	1.000	1.000	0.986	1.000	1.000	1.000	1.000
liquid	liquid	solid	liquid	gaseous	liquid	liquid	liquid	liquid	liquid

Stream Table

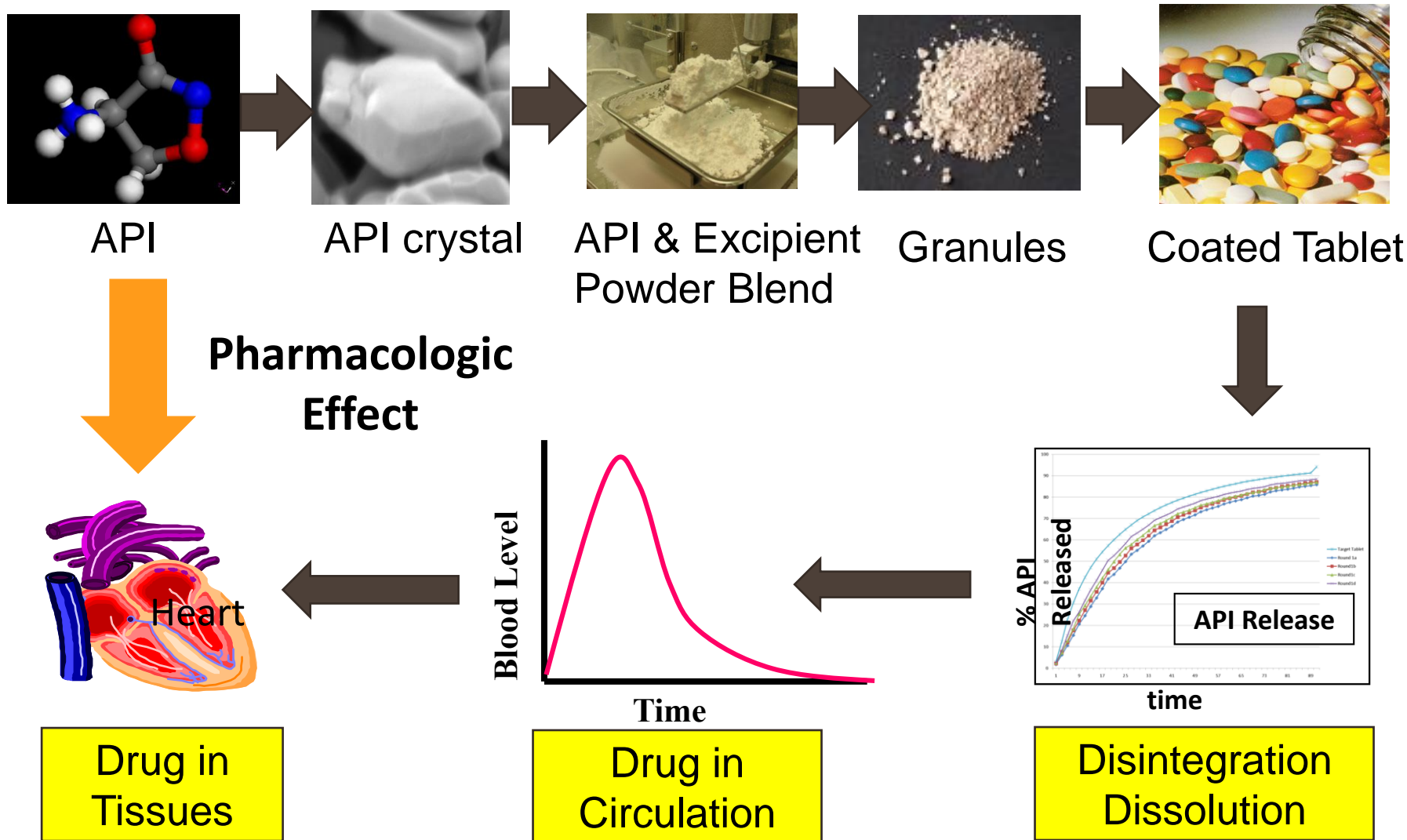


Means-Ends-Analysis & Non-Monotonic Planning

## Most Pharma Products are Formulations

- *Component Selection*
  - Active Pharmaceutical Ingredient
  - Non-therapeutic functional ingredients (excipients)
    - Stabilize API
    - Enhance manufacturing
    - Facilitate/regulate delivery
    - Protect product
- *Factors affecting immediate product performance*
  - Processing conditions
  - Formulation properties impacting delivery
  - Patient response: pharmacokinetics/pharmacodynamics
- *Factors affecting longer term viability*
  - Chemical / Physical Degradation

# PRODUCT DESIGN: TABLET



# PRODUCT DESIGN CHALLENGE

- **Goal:** Industry-wide use of knowledge- & model-based tools for product design
- **Barriers**
  - Formulation complexity (e.g., tablet, injection)
  - Estimation of formulation physical properties
  - Prediction of performance in vivo
- **Strengths**
  - Development groups now laced with ChE's
  - Growth of PSE product design research  
(Gani & Ng, Comp Chem Engr, 81, 70 (2015); Fung et al, ibid 91,15(2016))
  - Advances in GI tract, PBPK & tissue transport models  
Heitzig et al Comp Chem Engr, 71, 677 (2014)
  - Early work by Stephanopoulos group on iterative approaches to product (molecule) design  
Joback & Stephanopoulos, FOCAPD 1989

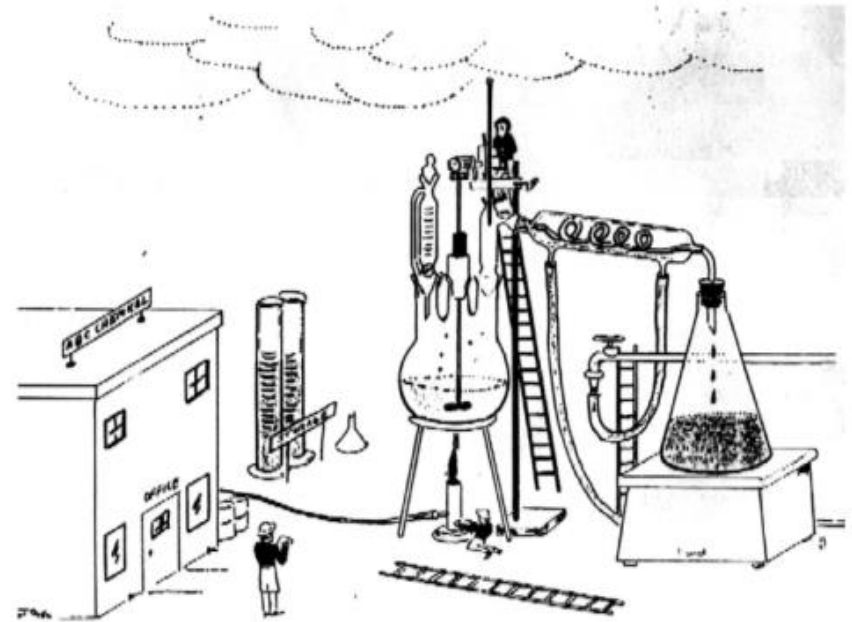
## CURRENT STATE

- Dominance of **Batch** operations
  - Progress in on-line sensing (PAT) adoption
  - Slow movement from passive monitoring to active control
  - Limited optimization-based scheduling methodology
- Recent attention to **Continuous** Processing
  - Significant progress in continuous solid oral dosage
  - Growing attention in small molecule actives manufacture
  - Limited progress in biologics manufacture
- Emerging Manufacturing Innovations
  - Point of use manufacturing
  - Mini-manufacturing systems (e.g., microfluidics)  
Adamo et al, *Science* 352, 6281, pp.61-67 (2016)



## Old-style Process Design & Plant Implementation

- Process chemists develop feasible lab recipe
- Engineers given scope for some improvements
- Process package transferred to manufacturing sites
- Manufacturing scale-up occurs by trial & error adaption to site equipment
- Continuous improvement limited due to concerns with change control regulations



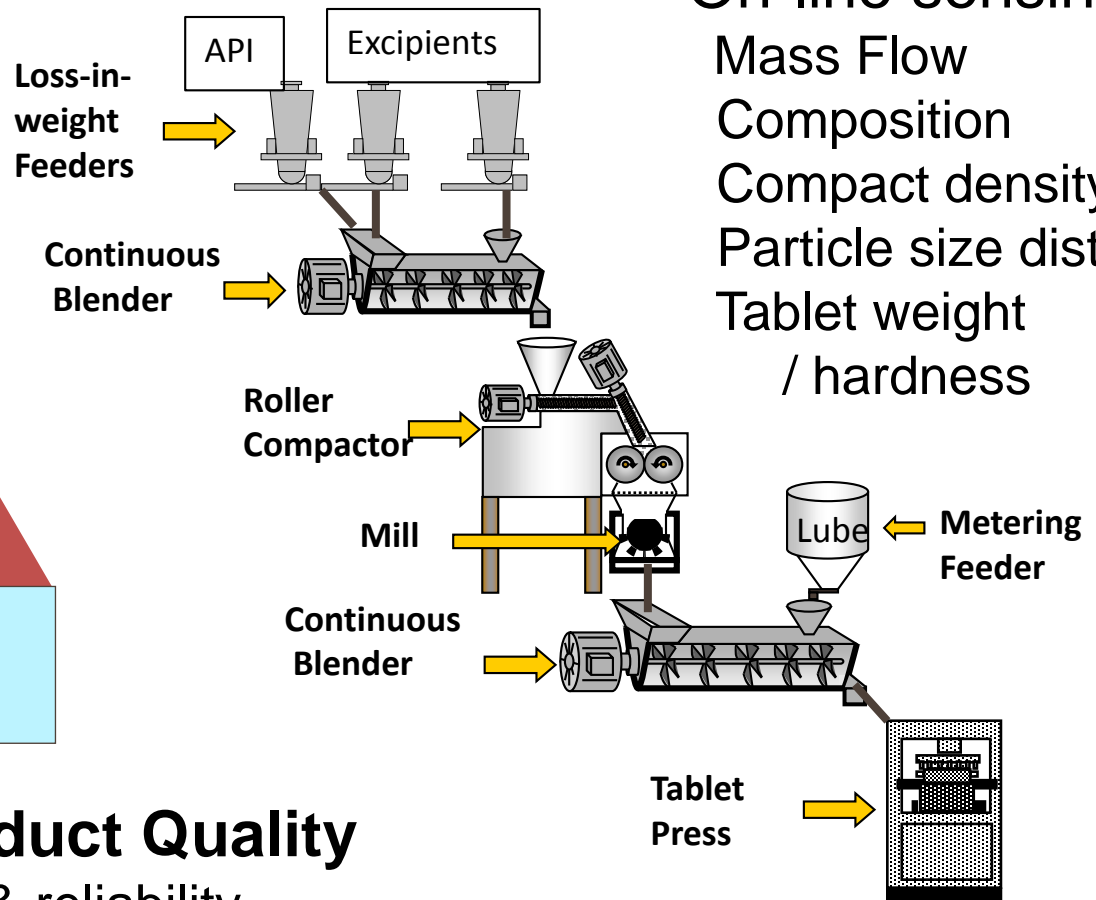
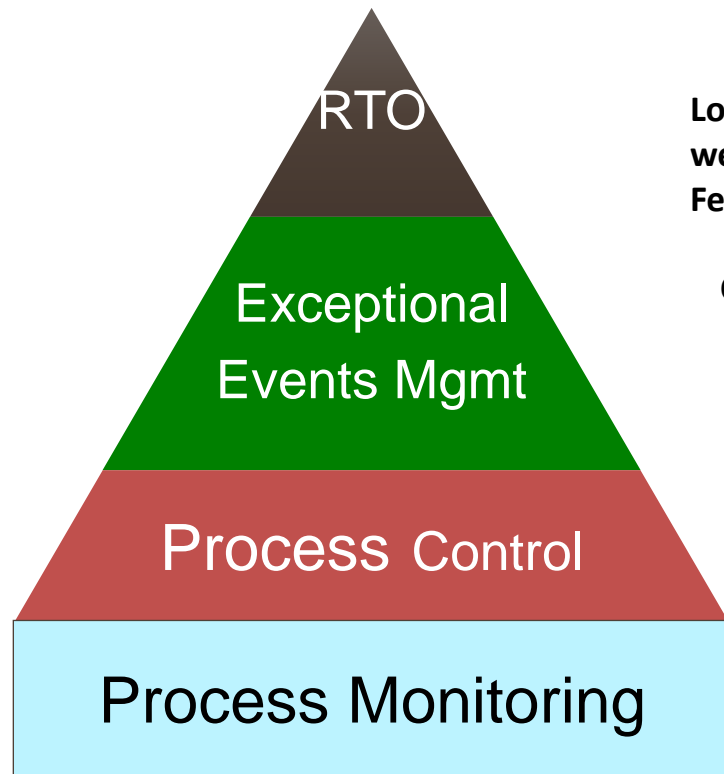
“The bench scale results were so good that we by-passed the pilot plant.”



# BATCH MANUFACTURING CHALLENGE

- **Goal:** Adoption of *Integrated Supervisory Control-Scheduling methods across industry*
- **Barriers**
  - History of quality by inspection
  - Limited on-line measurement & automation practice
  - Lack of trained plant personnel
  - Modeling & computational complexity
- **Strengths**
  - Development groups now laced with ChE's
  - Growing integration research by PSE community
  - Highly capable dynamic modeling & optimization tools
  - Foundational research by Stephanopoulos group on design of batch operating procedures (Lakshmanan, 1988-90)

# CONTINUOUS PROCESSING: REAL TIME PROCESS MANAGEMENT



## Key FDA concern: **Product Quality**

Sensor network design & reliability

Fault Diagnosis

Nonconforming materials segregation

Ierapetritou et al, *AIChE J*  
62, 1846-1862 (2016)

# CONTINUOUS PROCESSING CHALLENGE

- **Goal:** *Adoption of CM with model-based Real Time Process Management across industry*
- **Barriers**
  - Excess capacity in conventional batch facilities
  - Lack of clarity on business case for continuous processing across product types & business sectors
  - Slow vendor progress in tailoring automation applications
  - Lack of trained plant personnel
- **Strengths**
  - Regulatory agencies encouraging transition
  - Corporate awareness of transition to continuous
  - RTPM technology component research well developed
  - Extensive work by Stephanopoulos group towards RTPM:

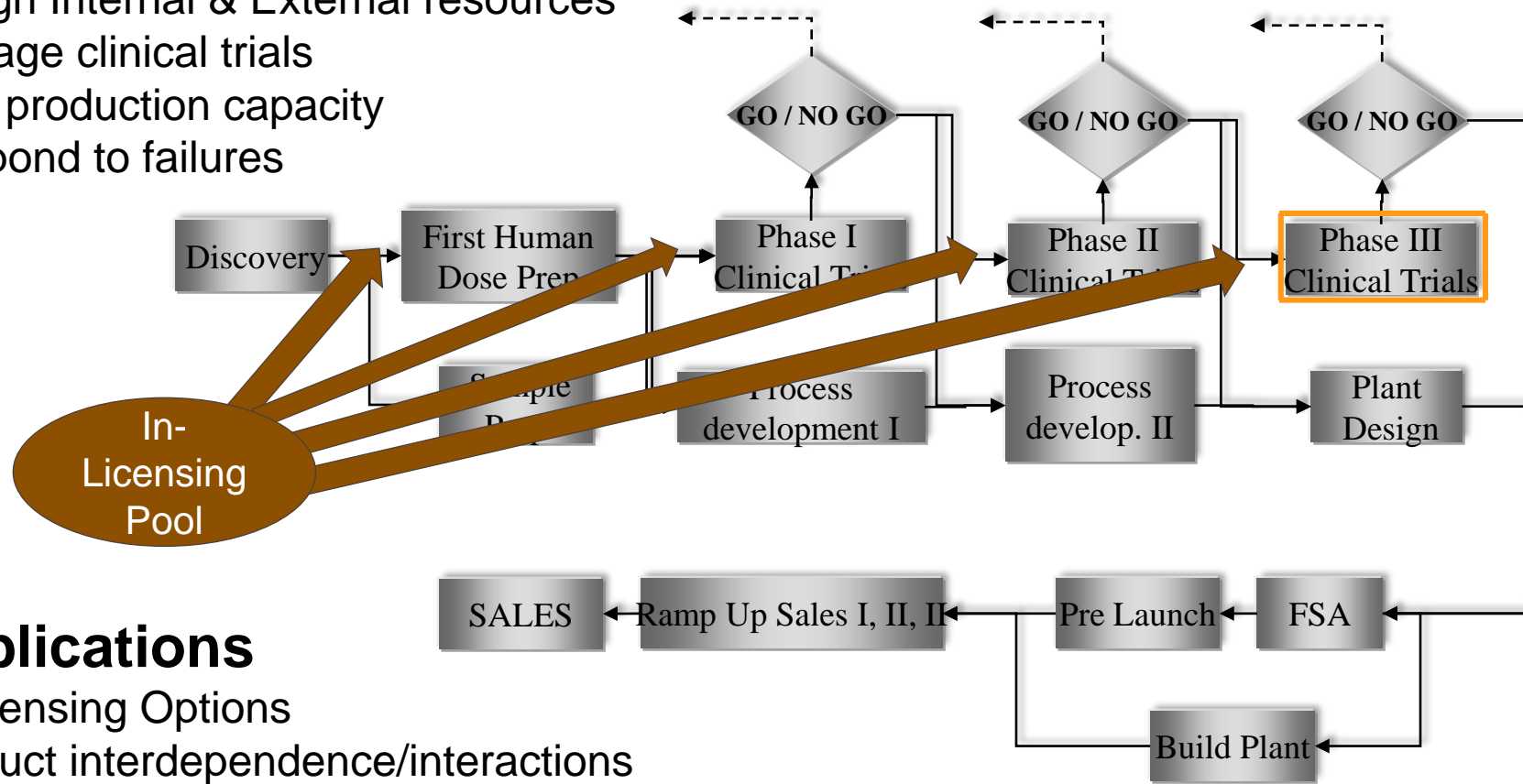
*Process monitoring, data reconciliation, trend analysis, fault diagnosis, & control system implications  
(Alvarez, Bakshi, Cheung, Romagnoli (1980-1995))*

# OUTLINE

- Current Context
- Challenges for 2040
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## Customary Decisions

- Select Products
- Assign Internal & External resources
- Manage clinical trials
- Plan production capacity
- Respond to failures



## Complications

- In-licensing Options
- Product interdependence/interactions
- Integrate Adaptive Trials with clinical supply chain
- Manage portfolio across therapeutic areas

# PRODUCT DEVELOPMENT PIPELINE MANAGEMENT CHALLENGES

- **Goal:** *Adoption of quantitative PDPM decision support tools by most major companies*
- **Barriers**
  - Limited history of model-based enterprise decision support (MBE) & integrated enterprise decision support (IEDS) systems
  - (Models) & require in-depth expertise multi-stage stochastic programs
- **Strengths**
  - Development cost escalation in unsustainable
  - Recognition that integrated information systems are needed to power informed decisions
  - Transition to adaptive clinical trials requires responsive supply chain
  - MSSP & PDPM research given growing attention by PSE community

## Need: Reduce Preventable Adverse Drug Events (ADEs)

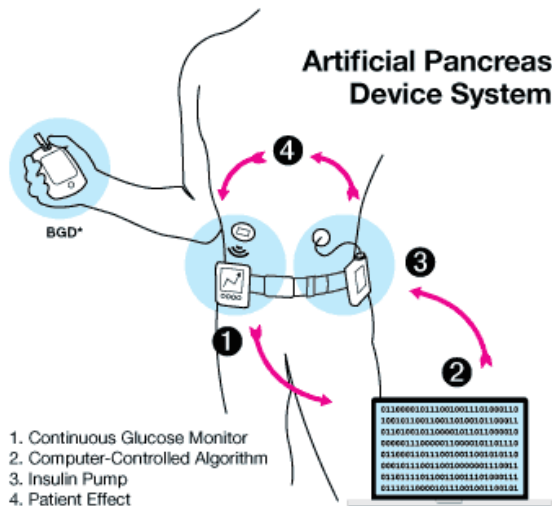
- *50% US population uses medications (25% children, 90% elderly)*
  - Individuals using multiple medications doubled 1990-2008<sup>1</sup>
  - Growing prevalence of narrow therapeutic index drugs
- *ADEs common & associated with poor medical outcomes*
  - ~400,000 events/y in hospitalized patients<sup>2</sup>
  - 5.3% of Medicare patient hospitalization<sup>2</sup>
  - Despite effort, 50% increase in ADEs 2000-2008<sup>2</sup>
  - Consequence: increased length of stay, increased mortality<sup>2</sup>
  - ADEs can cost 700-bed hospital over \$5.6 M/y <sup>3</sup>
- *Goal of Preventing ADEs and optimizing medication use featured*
  - 2014 National Action Plan, ODPHP
  - 2012 Learning Health Care System report, Institute of Medicine

# INDIVIDUALIZED DOSING CONCEPT

## Individualization Ideal

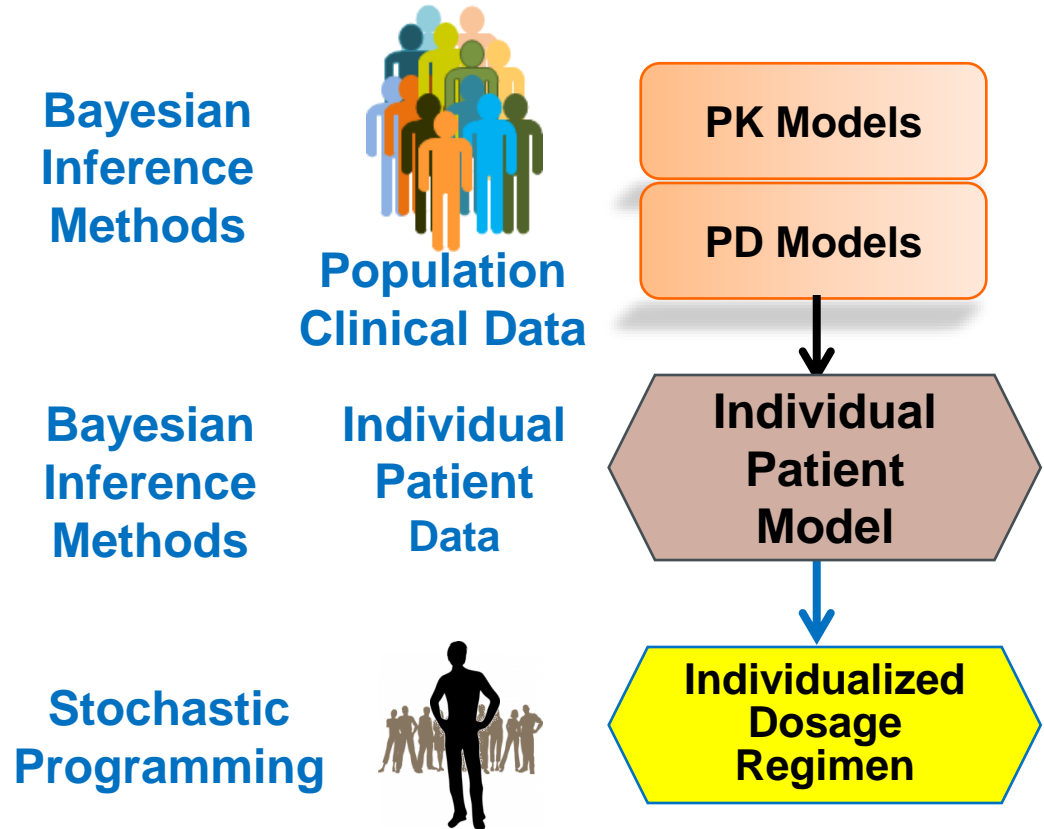
### Artificial Pancreas:

Closed-loop insulin dosing via glucose sensor, MPC model & insulin pump



Pintser et al, Diabetes Care, 2016

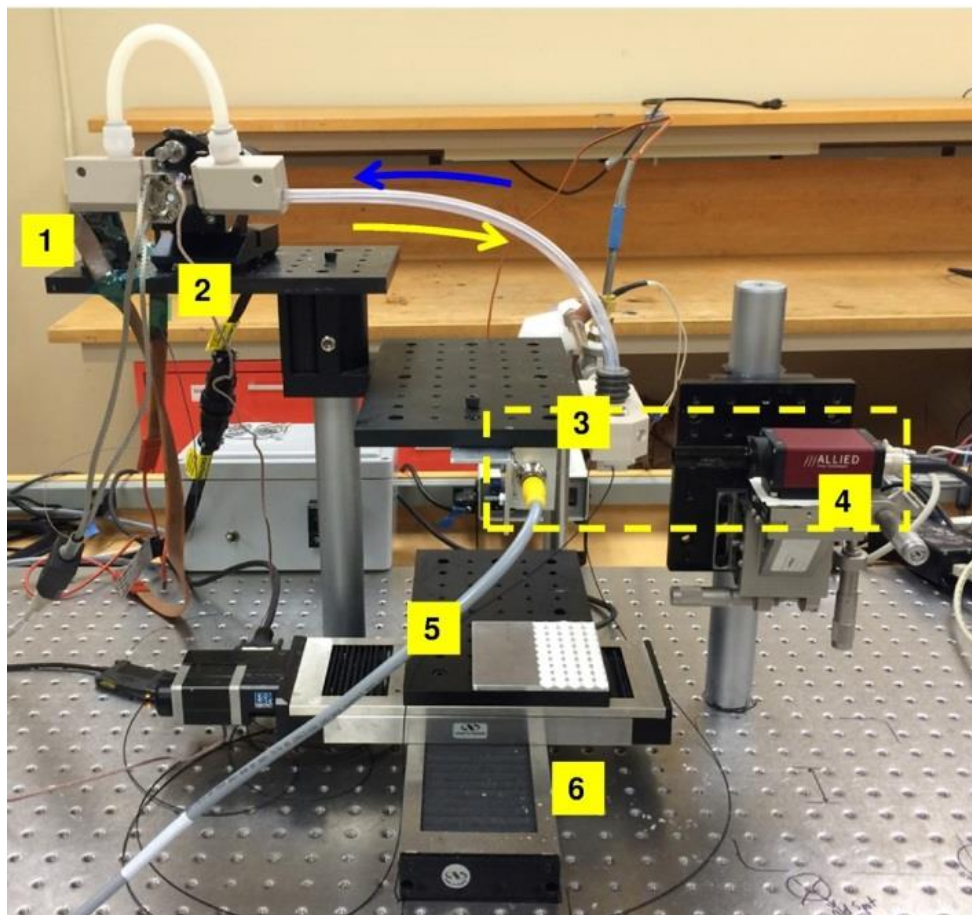
## Physician-in-the-loop model



Jayachandran et al *PLOS ONE* (2015);  
Lainez-Aguirre, et al *Technometrics* (2015)  
Abbate & Manca, *Comp Chem Engr* (2016)



## PharmaPrinter™ : Drop on Demand Dose Manufacture



Icten et al *I&EC Research* 55 (36), 9676–9686 (2016)  
Icten et al *Int J Pharmaceutics*. 524, 424-432 (2017)

### Components

1. Material reservoir
  - solutions
  - polymer melts
  - suspensions
2. Precision P/D pump
3. Nozzle
4. Camera & online imaging system
5. Dose substrate
  - inert tablets
  - capsules
  - films
6. xy-stage
7. Temp & form controls (not shown)

# INDIVIDUALIZED MEDICINE CHALLENGE

- **Goal:** *Individualized Medicine adopted in most pediatric & oncology clinics*
- **Barriers**
  - Blood sparing sampling & rapid analytical methods
  - Fast Bayesian & stochastic optimization methods
  - Reduced order predictive models with relevant covariates
  - Cost of prospective clinical studies
- **Strengths**
  - Clinician recognition that ADEs constitute critical problem
  - Growing penetration & use of eMedical Records
  - Beginning acceptance of web-based clinician advisory systems
  - Dosing predictions demonstrated with retrospective clinical data
  - Innovations in flexible dosing technology being commercialized



# CONCLUDING REMARKS

- Healthcare sector is fertile PSE application domain
  - Services need PSE decision support tools
  - Individualized medicine = decision support benefitting patient, clinician & healthcare system
- Improvements in drug cost, quality & availability are powerful driver for PSE developments in
  - Process synthesis, Product design
  - Advanced manufacturing, Product Pipeline management
- Foundation in PSE methodology built by George & PSE community makes 2040 goals achievable
- George & present company - ***make sure you are all still around to benefit!***

# EXCELSIOR!

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OF CHEMICAL ENGINEERING

**Best Wishes  
on your 70<sup>th</sup>  
Birthday !!!  
and  
for a Fulfilling  
& Optimized  
Retirement !!!**

