Innovations in Development of Synthetic Small Molecule Drug Substance

Jean Tom

Bristol-Myers Squibb – Chemistry Development

With input provided from:

Small Molecule Drug Substance Development

- State of Small Molecules
- Route Innovation, Process Innovation, Process Characterization
- Route Innovation – New Chemistry/Tools
- Process Innovation - Continuous
- Process Characterization – Digitilization/Use of Data and Modeling
- Introduction of Technology at Manufacturing
- Regulatory Implications
- Precompetitive Collaboration

(1) potential pharmaceutical applications of emerging technologies,

(2) key technical issues that will affect innovation,

(3) **regulatory issues for which the agency might want to prepare,**

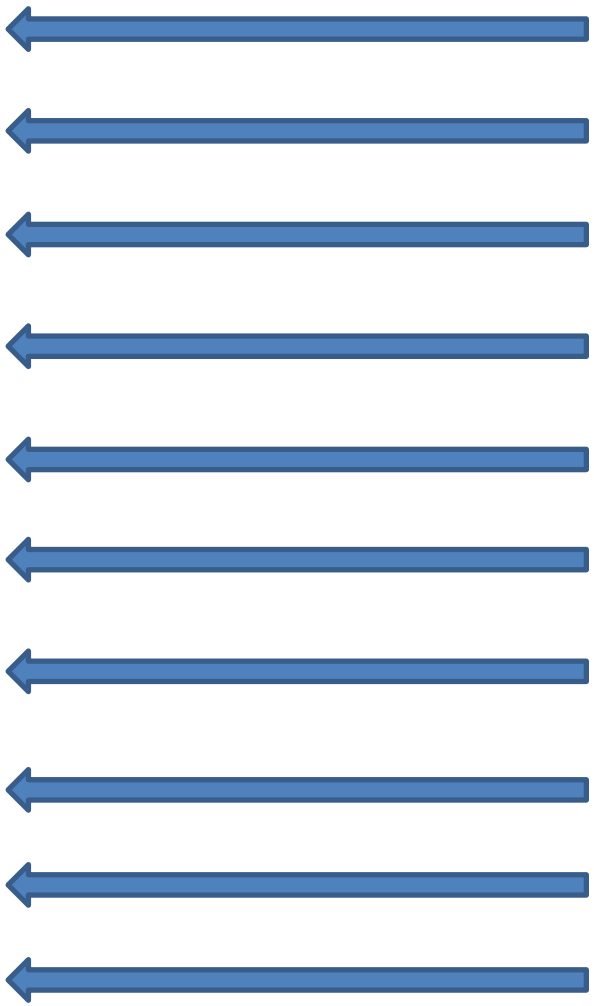
(4) suggestions for how to overcome those regulatory issues to facilitate the adoption of promising novel technologies in the pharmaceutical industry.

Top 10 sales generated in 2018

1. adalimiumab (Humira) – $19.9B
2. apixaban (Eliquis) - $9.9B
3. lenalidomide (Revlimid) – $9.7B
4. nivolumab (Opdivo) - $7.5B
5. pembrolizumab (Keytruda) $7.1B
6. etanercept (Enbrel)- $7.1B
7. trastuzumab (Herceptin) - $7.0B
8. bevacizumab (Avastin) - $6.8B
9. rituximab (Rituxan) - $6.7B
10. rivarixaban (Xarelto) - $6.6B

Top 10 most prescribed drugs

1. Vicodin (hydrocodone/acetaminophen) -Pain
2. Simvastatin (Generic for Zocor) – Cholesterol
3. Lisinopril (Generic for Prinivil or Zestril) –ACE Inhibitor
4. Levothyroxine (generic for Synthroid) - Thyroid
5. Azithromycin (generic for Zithromax, Z-PAK) - Antibiotic
6. Metformin (generic for Glucophage) - Diabetes
7. Lipitor (atorvastatin) - Cholesterol
8. Amlodipine (generic for Norvasc) – Calcium Channel Blocker
9. Amoxicillin - Antibiotic
10. Hydrochlorothiazide –Diuretic



https://www.medicinenet.com/top_drugs_prescribed_in_the_us/views.htm

2019 FDA Drug Approvals (102)

Synthetic Molecules	Total=70
New Small Molecules	41
New Formulation of previously approved small molecules	14
New Combination of previously approved small molecules	10
New indication for previously approved molecules	3
Nucleic Acid Molecules	2

Biologic Molecules	Total=29
Biosimilars	12
Antibodies (monoclonal, single chair, whole)	5
Vaccines	3
Recombinant Protein	5
Gene Therapy	1
Peptide Hormones	4

Synthetic/Biologic	Total =3
Antibody-Drug Conjugates	3

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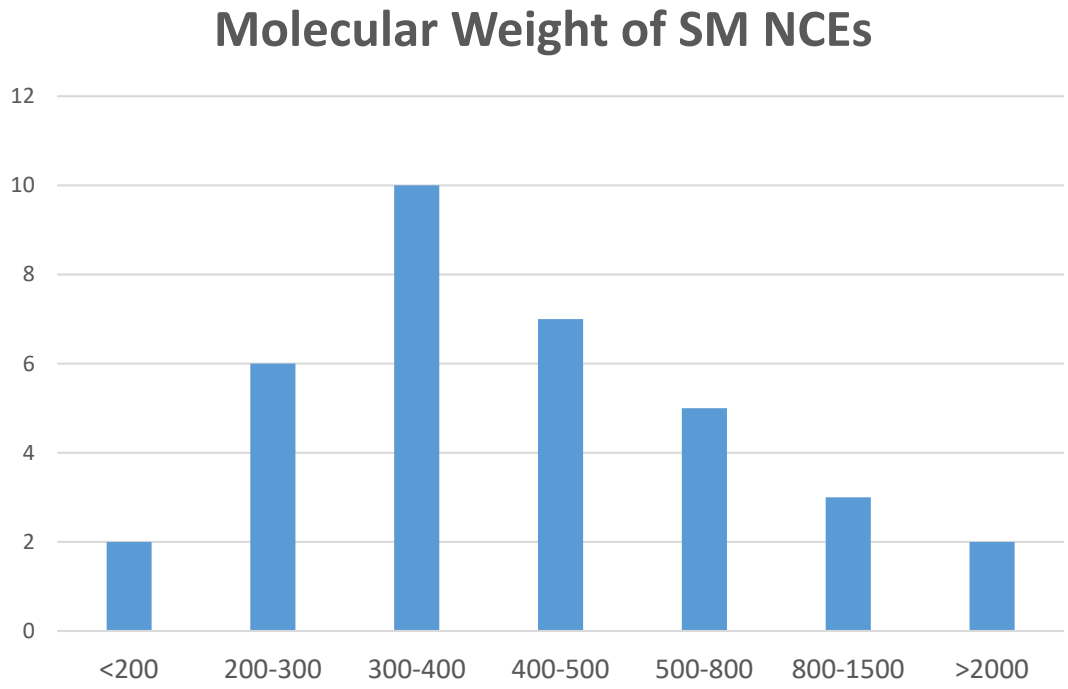
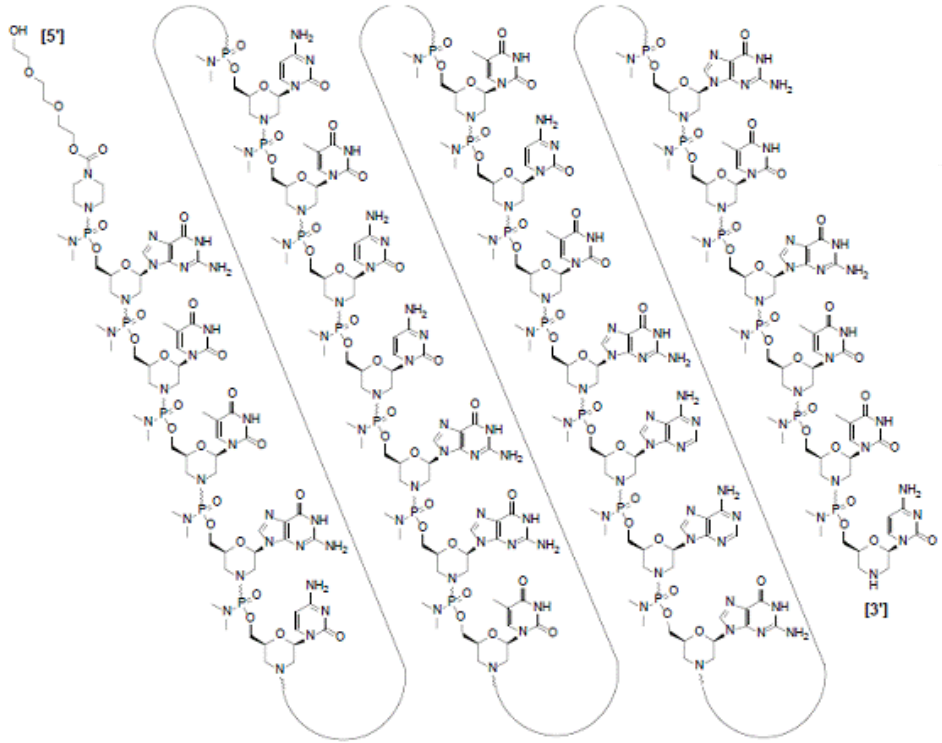
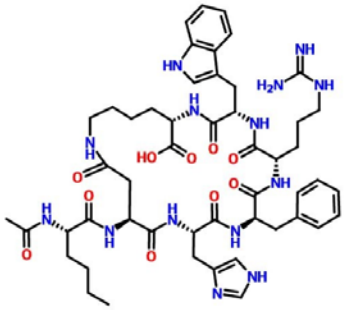


Synthetic/Biologic	Total =3
Antibody-Drug Conjugates	3

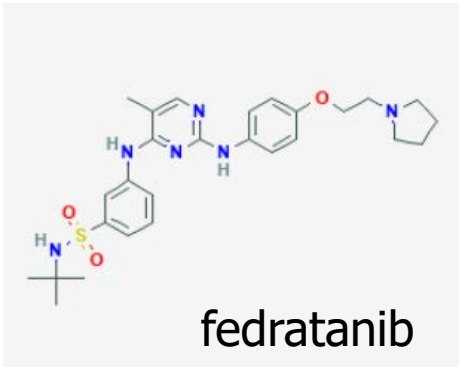
Molecular complexity



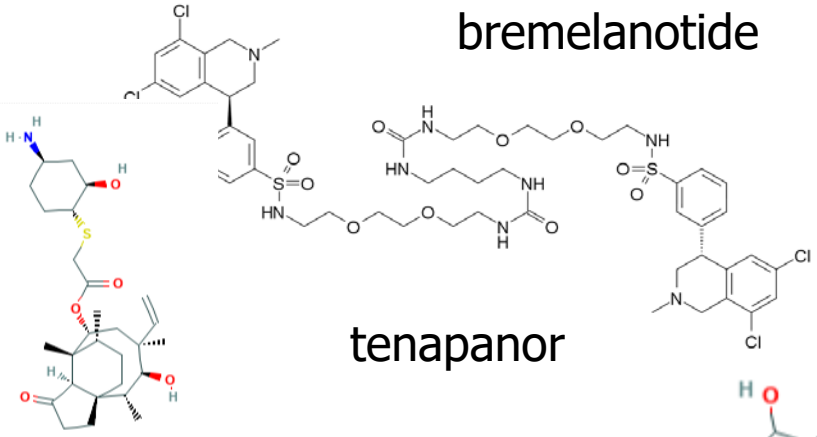
Golodirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass with molecular weight of 8647.



bremelanotide

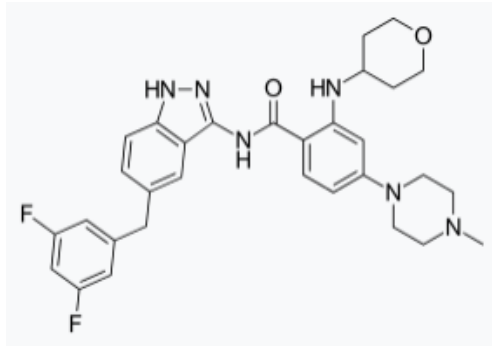


fedratanib

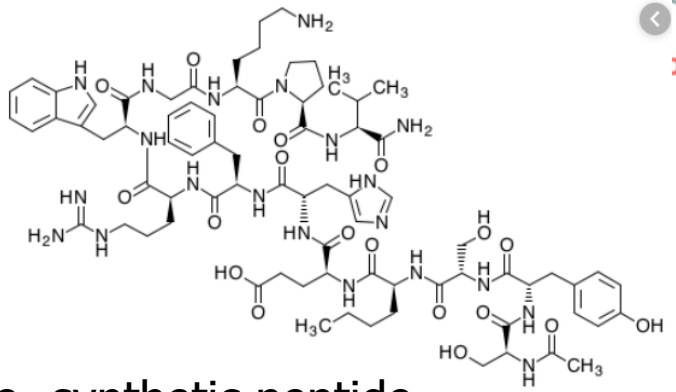


tenapanor

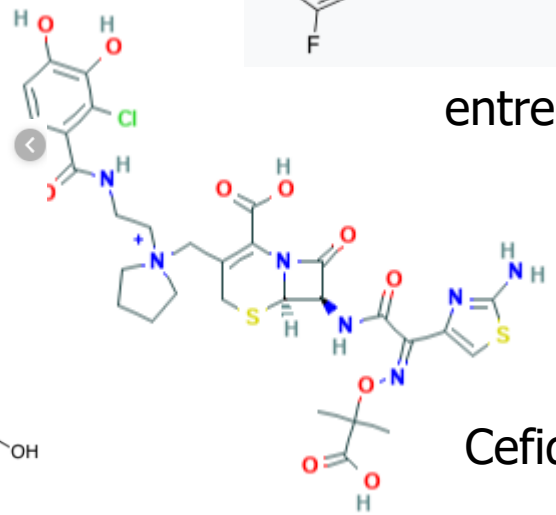
lefamulin



entrectinib



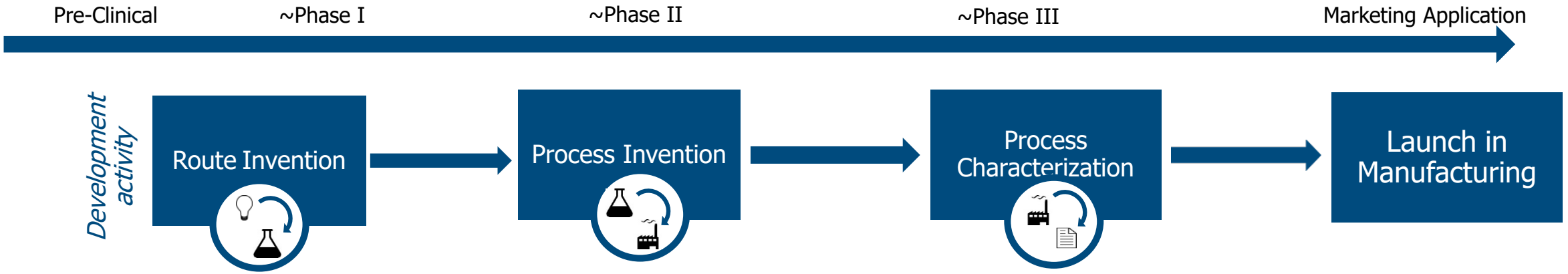
Afamelanotide -synthetic peptide



Cefiderocol,

Stages of Process Development for Synthetic Small Molecules

- Goal: Invent and develop safe, phase appropriate, efficient, sustainable, and economically viable processes for the manufacture of drug substances (from commodity Starting Materials (SM) to API)



- Determine the synthetic route
  - commodity chemical SMs and intermediates to make API
  - Using chemistry to enable most direct approach
  - Safety, Sustainability, Robustness, Cost
- Turn the synthetic route into the commercial process
- Selection of class variables (reagents, solvents)
- Selection and optimization of the series of unit operations
- Designing the process for simplicity and robustness from the ground up
- Finalize the commercial process
  - Process parameter ranges
  - Control strategy
- Innovative experimentation, modeling, and analysis
- Process Validation

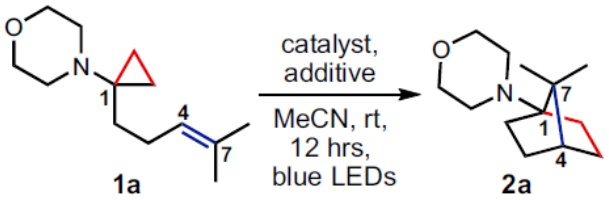
Innovation in Route Invention - Chemistry

- Chemistry
  - Photochemistry
  - Electrochemistry
  - Biocatalysis
    - Cascade catalysis
- Large Complex Molecules
  - Peptides, Oligonucleotides
  - Molecules with "catalytic" binding functions (Proteolysis targeting chimera-PROTAC; protein degradomers)
  - Chemically labile by design (prodrug)
- Co-Processed API

Photochemistry in Small Molecule Synthesis

Why photochemistry?

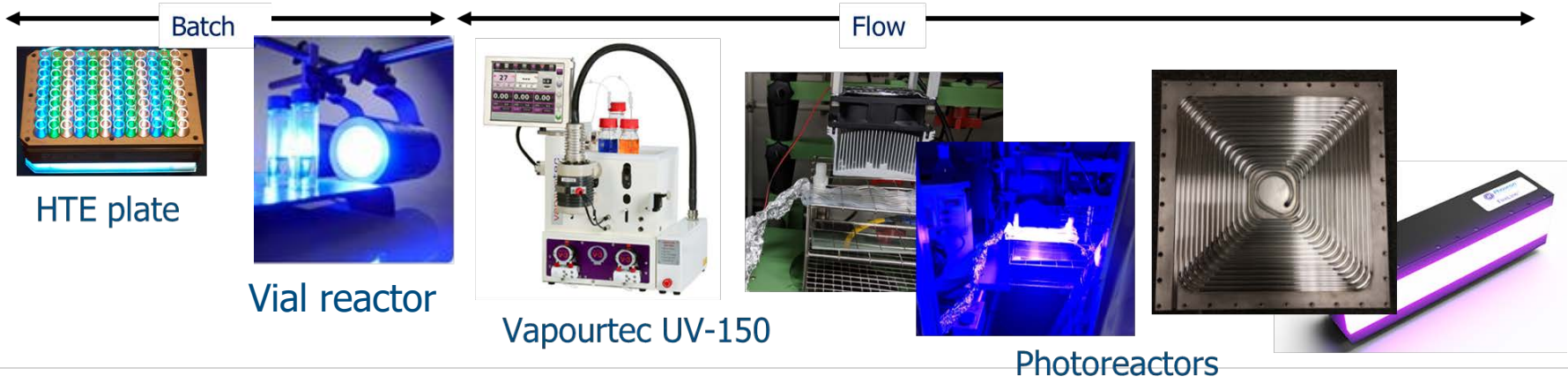
- New bond-forming methodologies expand the synthetic toolbox
- Easy access to complex molecular scaffolds with stereoselectivity (*e.g.,* highly strained molecules, increasing the saturation)
- Improving the greenness of the current synthetic routes



D. Staveness, *et al. Chem,* ***2019,*** 5, 215

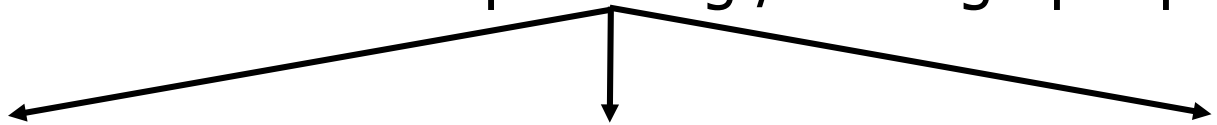
Drivers for utilizing visible light

- New photocatalysts that harness lower-energy visible light enable the selective activation of specific functional groups while minimizing background reactivity
- Advances in LED technology: lower energy consumption, longer lifetime, improved physical robustness, smaller size, and faster switching



Optimizing/scaling up

Parameters to consider when optimizing / scaling up a photochemical reaction



General reaction parameters

- Solvent
- Concentration
- Additives / catalyst
- Temperature
- Heat transfer
- …

Radiation-related reaction parameters

- Wavelength-dependent quantum yield
- Molar extinction coefficient of the reaction species
- Wavelength selectivity of the desired reaction
- …

Reactor-related parameters

- Light source wavelength
- Light source intensity
- Reactor geometry (light distribution)
- Photon flux on the reactor walls
- Reactor material / medium absorbance
- Heat transfer
- Mixing
- Chemical compatibility
- …

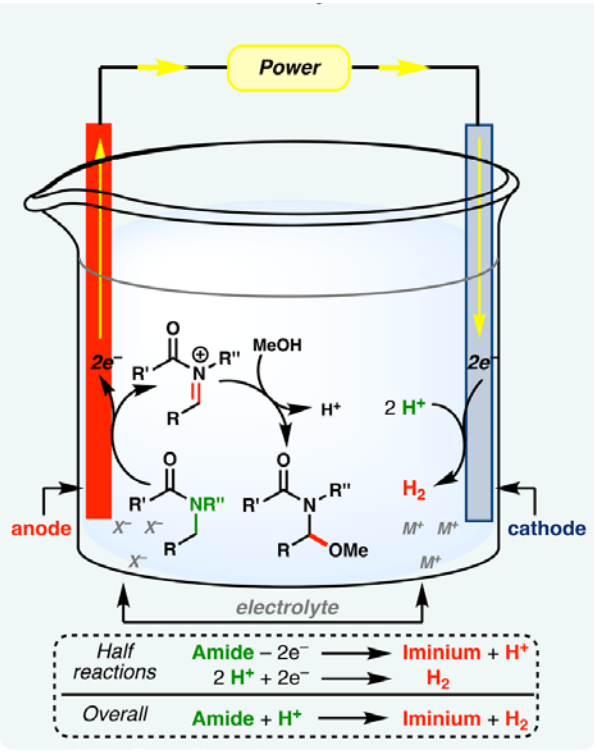
Most of these parameters are coupled

We need to combine experimental methods with modeling to decouple these parameters and enable transferability of photochemical processes across different platforms / scales

Electrochemistry in Small Molecule Synthesis

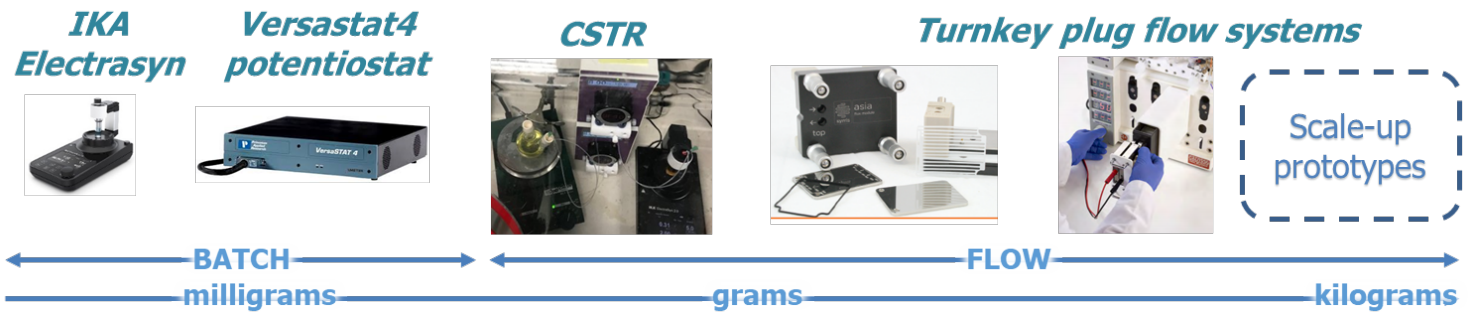
- **Mild reaction conditions**
- **High chemoselectivity**
- **Tunability**
- **Versatility**
- **Greenness**

- C-N coupling and heterocycle formation reactions
- Oxidation chemistry
- Fluorination or other late stage functionalization reactions



Chem. Rev. **2017**, 13230

Challenges in batch	Applicable continuous technology	Design capabilities in flow
• Scalability limits of electrodes • Reactor geometry affects electronic environment • Mass transfer limitations • Non-conductive reactor elements required	• Plug flow reactors between electrode plates • CSTR of multiple batch reactors	• Small gap between electrodes reduces electrolyte need • Reduced mass transfer limitations • Predictable reaction geometry and scale-up • Rapid screening of key parameters



Optimizing/scaling up of electrochemical reactions

Parameters to consider when optimizing / scaling up an electrochemical reaction

General reaction parameters

- Solvent
- Concentration
- Additives / catalyst
- Starting material
- Temperature
- Reaction pathway
- Reaction rate constant
- …

Electrochemistry-related reaction parameters

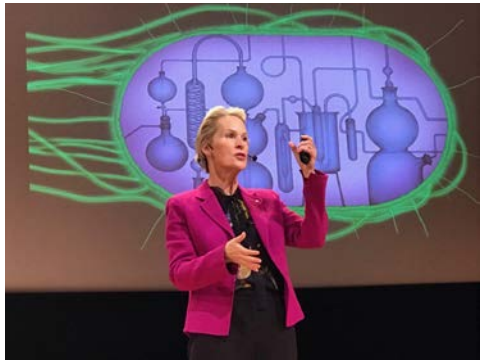
- Standard potential (E^o)
- Over-potentials
- Faradaic efficiency
- Electrolyte cation/anion choice
- Electrolyte concentration
- Resistance of the electrolyte
- Counter-electrode half reaction
- Variations in voltage/current with conversion (or distance in flow)

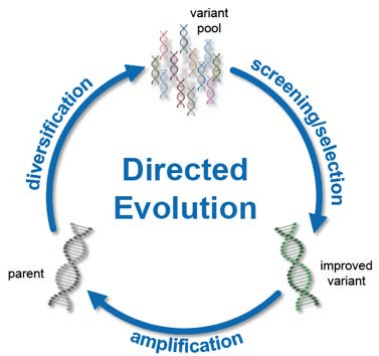
Reactor-related parameters

- Electrode material
- Electrode surface area
- Distance between the electrodes
- Applied potential/current
- Heat transfer
- Mixing
- Chemical compatibility
- …

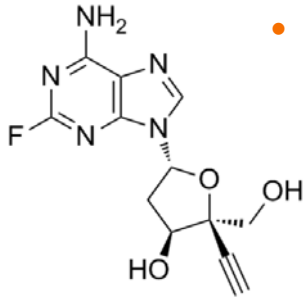
Most of these parameters are coupled

Biocatalysis in Small Molecule Synthesis





- **Directed evolution of enzymes**
- **de novo design of biocatalysts (directed evolution, advances in analytics, machine learning, and sequencing)**



- **Cascade Biocatalysis:** Mutiple enzymes and steps in a single pot from RSM to API (Merck: enzyme cascade to produce Islatravir)

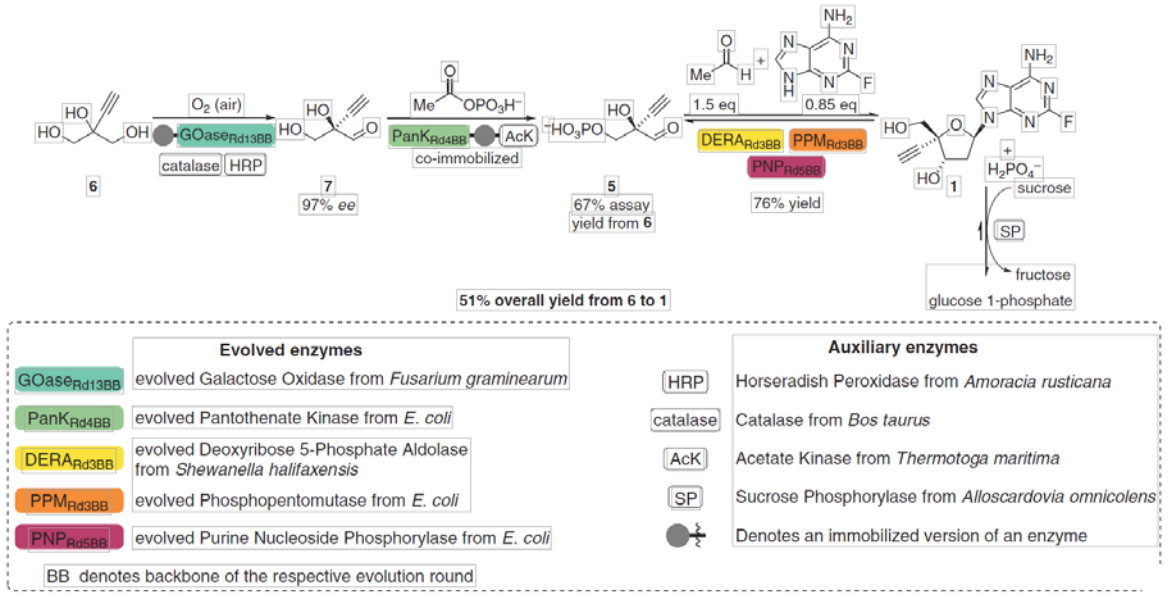


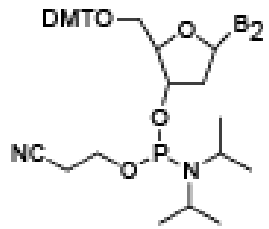
Fig. 2. Fully assembled biocatalytic pathway. Evolved enzymes are in colored boxes, and wild-type auxiliary enzymes are in white boxes.

Technical Challenges
- Complexity of reaction network
- Characterization of evolved enzymes to ensure high specificity
- Process control, characterization, and robustness of the cascades

Huffman *et al.*, *Science* **366**, 1255–1259 (2019) 6 December 2019

Large Complex Molecules

- Oligonucleotides
  - Single stranded DNA or RNA: Antisense oligonucleotides, siRNA (typically 15-30 bases in length)
  - Solid-phase synthesis using phosphoramidite method and phosphoramidite building blocks
  - Multiple chemical steps (detritylation, activation, coupling, oxidation, capping) – multiplicative effect on impurities



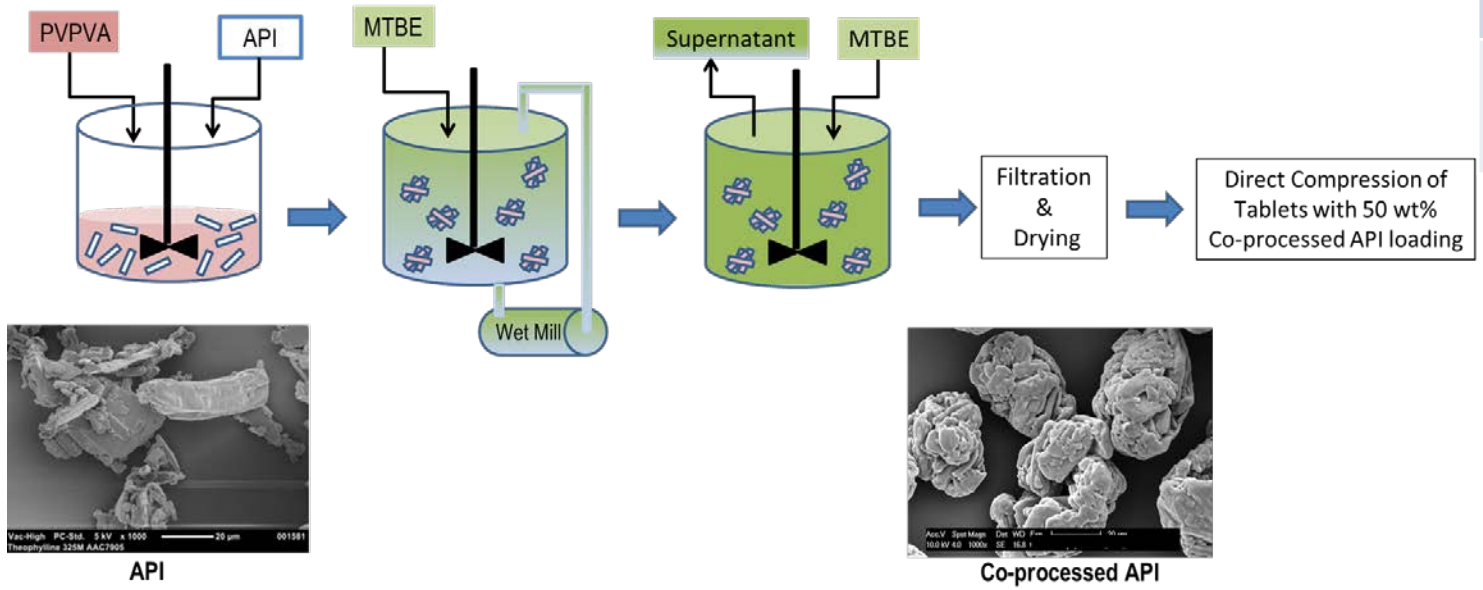
- Peptides
  - Hybrid phase synthesis; distributed solid phase for small components and solution phase to connect the components; membrane reactor systems
- Chemically labile by design (prodrug)
  - Impurities that transform or equilibrate prior to absorption
- PROTAC molecules – Proteolysis targeting chimera, Protein degradomers
  - "catalytic" binding functions compounds -two lipophilic substructures connected with linker

Regulatory challenges

- Comparability approach rather than typical small molecule impurity approach
- Treatment of impurities: grouping subsets of impurities, adjustment of limits of detection, and identification requirements – should be based on sound scientific arguments
- Analytical methods

Co-Processed APIs

Drug substance that contains the pharmacologically active ingredient in addition to one or more non-covalently bonded non-active component (additives, carriers excipients)



Reference: *Erdemir D. et al. "Design and Scale-up of a Co-processing Technology to Improve Powder Properties of Drug Substances" Org. Process Res. Dev. 2019, 23, 12, 2685-2698*

Routes to Generate Co-Processed API
Carrier Particles
Additive Mediated Crystallization
Combine API + Non-Active components via crystallization and/or precipitation-solvent based processes
Non-Active component (excipients) addition during API isolation

Ability to transform API physical properties to enable drug product manufacturing

- Robustnesss for batch processes
- Continuous Direct Compression
- Continuous End-to-End Drug Substance to Drug Product

Regulatory Implications of Co-processed API

- Classification as a Drug Substance vs Drug Product Intermediate
  - Drug Substance
    - Alignment with the equipment/capabilities in Drug Substance manufacturing facility (solvent-based processing)
    - Impurity profile, quality attributes, stability data studied and understood to enable appropriate specifications, control strategy
    - Enables retesting and reworking
  - Drug Product Intermediate
    - DP expiry determined based upon start of processing

A perspective paper on this topic entitled "Co-Processed API: A Proposed Regulatory Strategy to Enable Transformative Capabilities in Pharmaceutical Manufacturing" is being submitted for publication to ***Molecular Pharmaceutics*** in 1Q2020 by the International Consortium for Innovation & Quality in Pharmaceutical Development (IQ) API Working group

Process Invention – Continuous Processing

DRIVERS

- Safety: Chemistry at the extremes
- Robustness
- Productivity & process intensification
- New Chemical Methodologies: Electro-, photo-, immobilized catalysts
- Future focus of Pharma 4.0

TECHNICAL CHALLENGES

- Process control and characterization from across scales and equipment
- First principle understanding

  Physiochemical relating to mechanism
- Real-time feedback loops and predictive modeling (fully autonomous?)
- Regulatory requirements for portable manufacturing skids

Innovations in Process Characterization

- Easy access to computational power and open source codes has enable more advanced data analysis and modeling
  - Empirical Modeling through Machine Learning
  - Mechanistic and Unit Operations Modeling
    - Kinetic, thermodynamic, mass transfer based models
  - Residence Time Distribution Models – Continuous Processing
  - Bayesian Statistics
    - Capture variability in models and processes
  - Combination models
- Enable use of small number of batches/data set to develop models which can provide significant insight for development of specifications and design space
- Look for consistent regulatory acceptance in data packages containing more (and potentially majority) model-generated results (vs. experimental results).

Data Analysis/Modeling Enabled by Recent Technologies

- Convergence of key technologies:
  - Statistical Programming Language R
  - Open source programming languages
- Cloud Computing
  - Cloud High Performance Computing
  - Domino Data Lab = computing + version control
  - Jupyter notebooks = modeling + documentation
  - Software sharing
- Advances in Bayesian Regression Modeling algorithms
  - rStan
  - Other libraries (`rstanarm`, `brms`, `loo`, `projpred`)

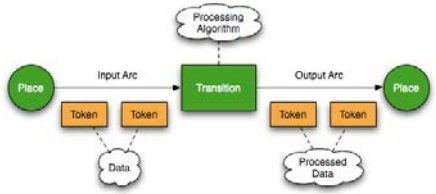
Bayesian Probabilistic Modeling

Inputs

Data

Mathematical Model

Statistical Model
(uncertainty, variability)

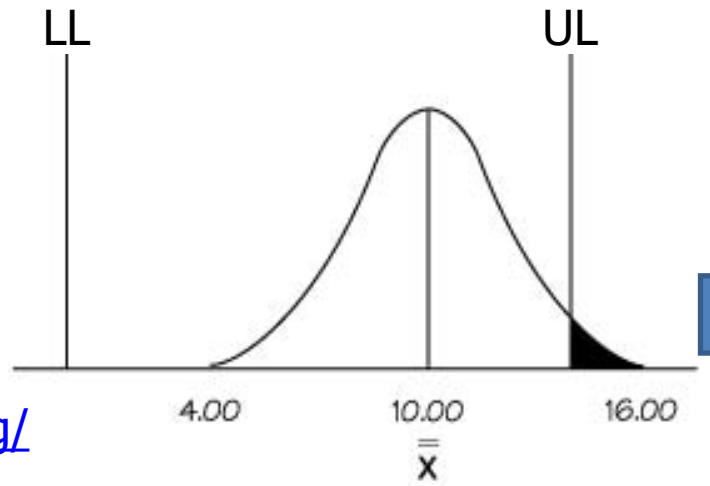


John J Peterson (2008) Journal of Biopharmaceutical Statistics, 18:5, 959-975

Stan

https://mc-stan.org/

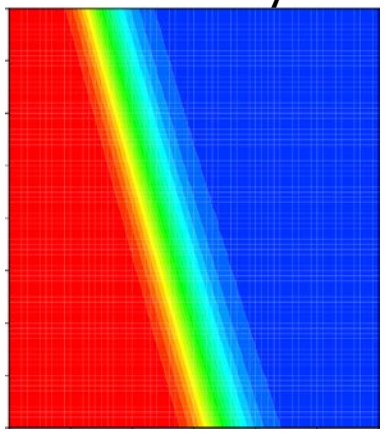
$Y=f(x)+e_y$



Capability Map

$\langle x: \Pr(\boldsymbol{Y} \in A|\boldsymbol{x}, data) \geq R \rangle$

R = Reliability



Overall variability

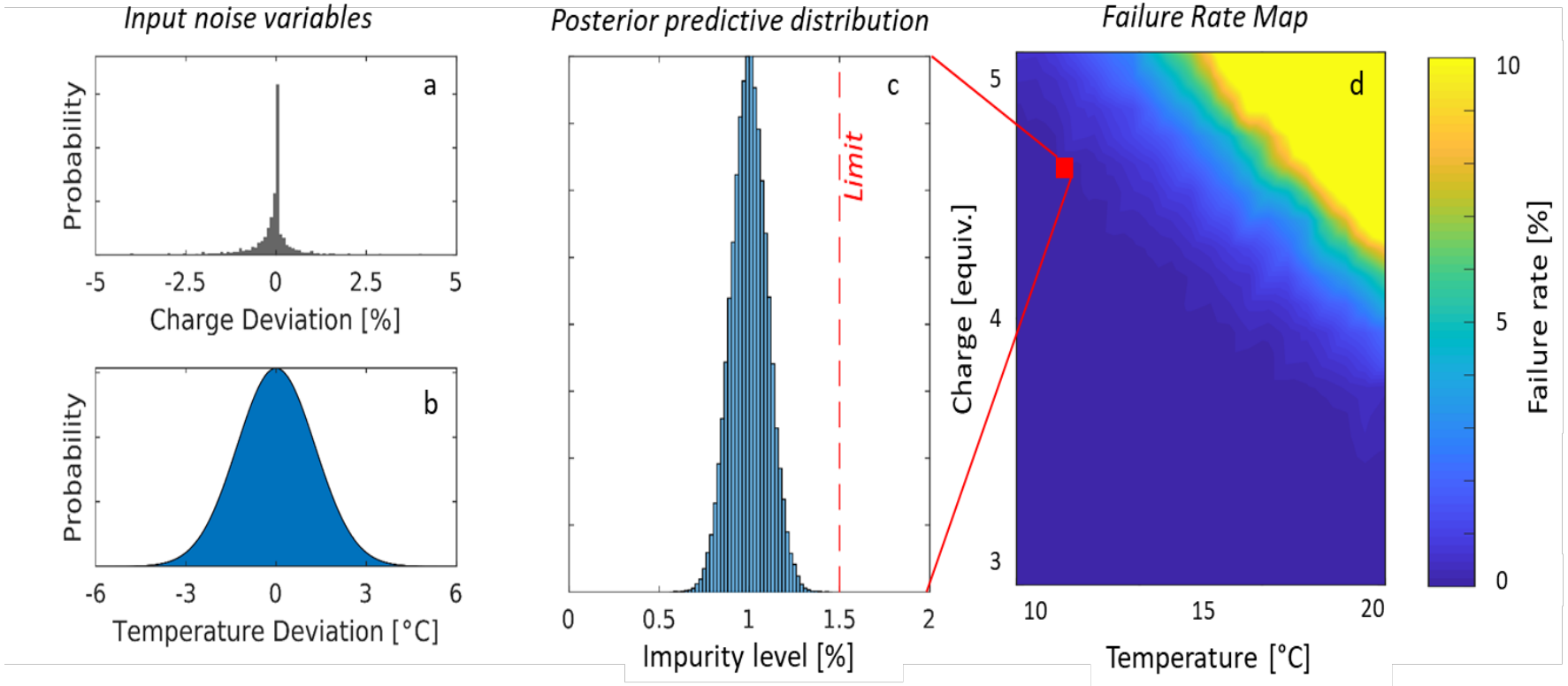
Process variability

Sample variability

Measure variability

Bayesian Probabilistic Modeling

$X = X_T + e_X$ $\quad Y = f(X) + e_y$ $\quad \langle x : \Pr(\boldsymbol{Y} \in A | \boldsymbol{x}, data) \geq R \rangle$

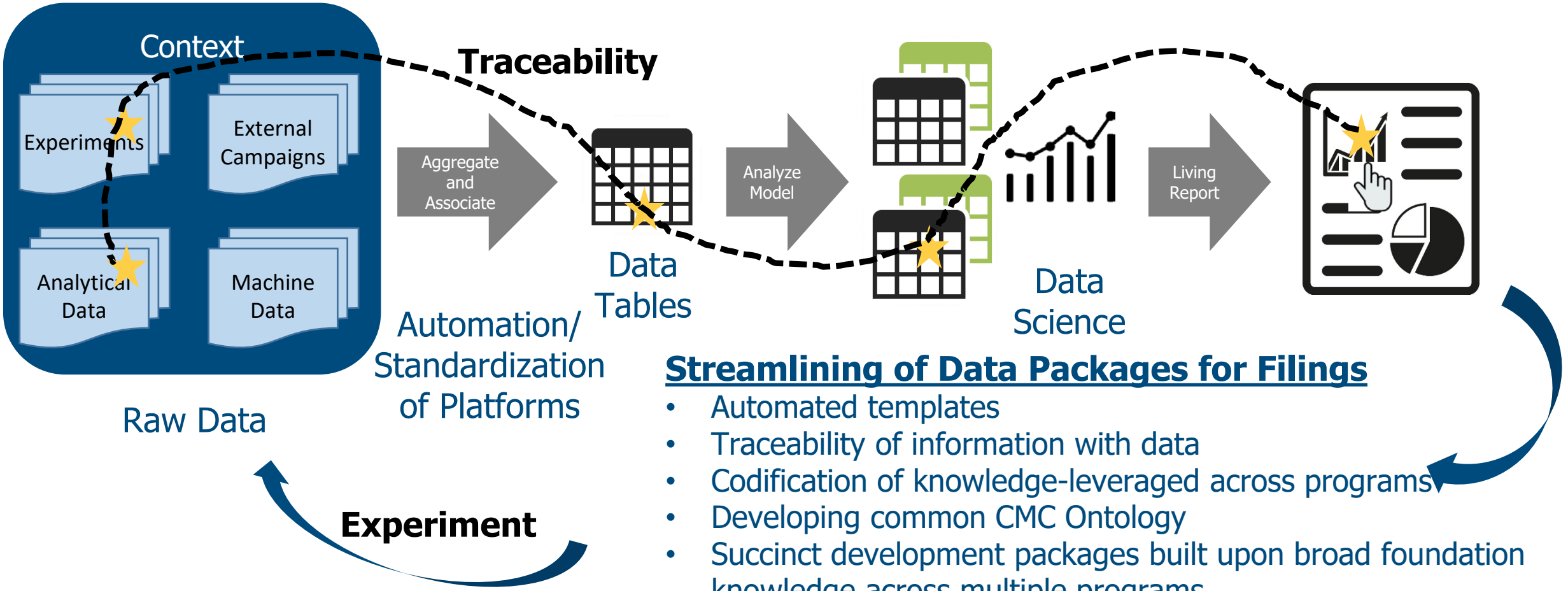


Framework where the limited process data generated during the development stage can be used to project risks, and establish controls to meet quality and robustness expectations upon product launch.

Tabora, J.E., Lora Gonzalez F., Tom, J. "Bayesian Probabilistic Modeling in Pharmaceutical Process Development" AIChE Journal, 2019, 65(11),

Automation and AI/ML based Development

Future State: An end-to-end digital, contextualized chain from data generation to consumption to reporting



Streamlining of Data Packages for Filings

- Automated templates
- Traceability of information with data
- Codification of knowledge-leveraged across programs
- Developing common CMC Ontology
- Succinct development packages built upon broad foundation knowledge across multiple programs
- Automated authoring/reviewing
- Support accelerated filings

Introduction of Technology into Manufacturing

- Acceptance of new technology dependent on manufacturing and quality organizations
- Some manufacturing and quality organizations tend to be resistant towards innovative technologies
  - Cost savings for new technology tend to be minimal
  - Lack of scale-up capacity/infrastructure in manufacturing networks; Example: Available capacity of standard batch equipment
    - Increasing externalization of manufacturing network
  - Culture and incentives may not be in place to support (flexibility)
- Changing manufacturing infrastructure
  - Single infrastructure to enable new modalities (small volumes) or modular units

Overall Regulatory Issues with emerging technologies

- There is not one unified world regulatory authority whose expectations are clear and consistent. We face scrutiny from many regulatory authorities with disparate views and expectations.
- While the FDA may support (or even advocate for) innovation at the senior leadership levels, reviewers tend to more conservative which translates to extra scrutiny and greater resistance when technologies are unfamiliar.
- Internal CMC groups become risk-averse because they understand the challenges and don't want to compromise filing timelines and create avoidable obstacles by bringing forward innovative processes that could get tripped up in any one of the very many reviews.
- There needs to be worldwide approach - as most products file in multiple markets - to avoid being limited by the most conservative approach. Would the committee be able to influence a holistic approach?

Industry Collaboration to Move Technology

A not-for-profit organization of ~42 pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community.

13 companies collaborating pre-competitively on issues related to pharmaceutical chemistry, manufacturing, and control with the goal of identifying, evaluating, developing, and improving scientific tools and techniques that support the efficient development and manufacturing of pharmaceuticals.

Informal precompetitive collaboration to share knowledge about continuous processing (DS/DP) approaches, questions, CMO technology

Over 100 member companies working Our projects transform R&D innovation through pre-competitive collaboration. We bring together the key constituents to identify the root causes that lead to R&D inefficiencies. We develop best practices and technology pilots to overcome common obstacles. Projects in Safety database, AI/ML, ontologies

40 member companies collaborating to develop advanced data architecture to transform the acquisition, exchange, and management of laboratory data throughout its complete lifecycle.

Opportunities for FDA to partner with these industrial collaboration

Summary – Small Molecule Drug Substance Development

- Relatively mature
- Accounts for large majority of new drug candidates
- High molecular complexity
- Innovations in this space
  - Enabling more direct approach to the molecule
  - Streamlining how data is both generated and presented to regulatory authorities
  - Challenging current thinking of how to evaluate robustness and control strategies

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- Erwin Irdam

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- Ahmad Sheikh

MERCK

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- Kevin Campos

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janssen
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