Accelerating Biopharmaceutical Development: Data-Driven Strategies, Platforms, and Technologies

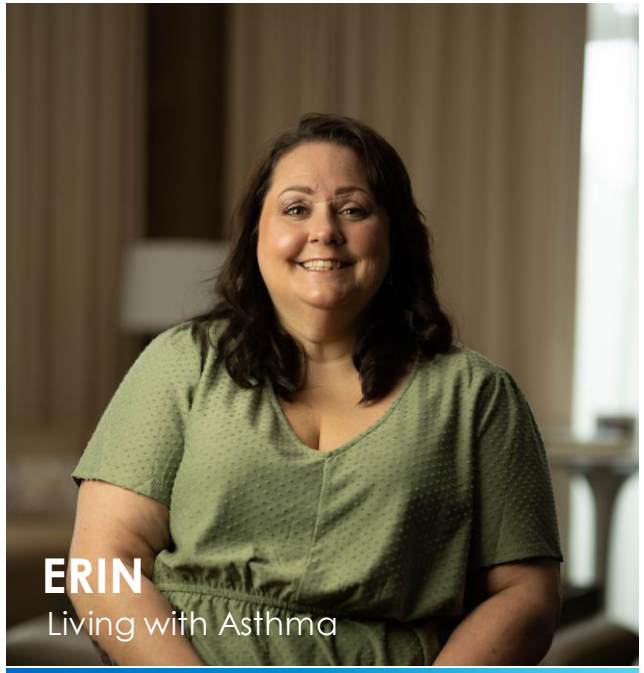
Nitin Rathore

Vice President, Drug Product Technologies, Amgen Inc.

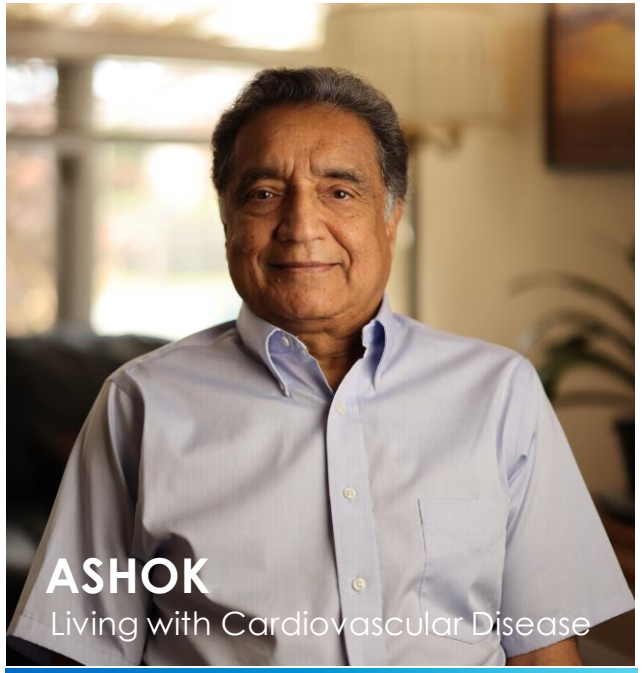
AMGEN®

Our Therapeutic Areas Focus

ONCOLOGY



INFLAMMATION



GENERAL MEDICINE

RARE DISEASE

We serve millions of seriously ill patients living with cancer, cardiovascular disease, inflammatory diseases and more.

AMGEN

Our Products Reflect Our Commitment To Serving Patients Living With Serious Illness

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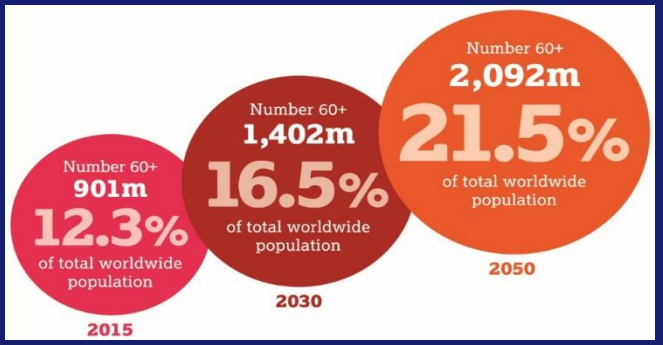
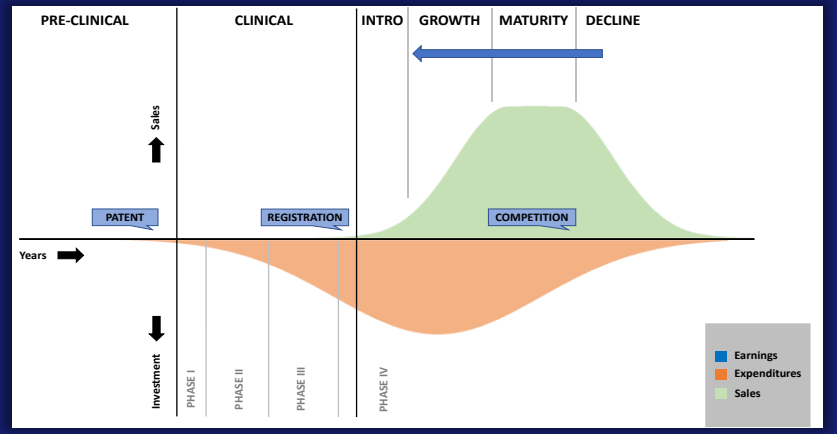
The evolving landscape we are operating in ….



BioSpace

CES HOTBEDS CAREER EVE

Faster Drug Development Processes Likely to Outlive COVID-19



WSJ The Wall Street Journal

Elevated Inflation Presents Risk to U.S. Economy, Fed Report Finds

NEWS

Inflation will have the biggest negative impact on pharma industry in 2023: survey

Forty percent of industry professionals cited inflation as the top challenge for the pharma industry in 2023, a recent GlobalData survey finds.

HEALTH AND SCIENCE

Passage of Inflation Reduction Act gives Medicare historic new powers over drug prices

PUBLISHED FRI, AUG 12 2022·5:42 PM EDT | UPDATED FRI, AUG 12 2022·8:37 PM EDT

Spencer Kimball @SPENCEKIMBALL

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yahoo!finance

The global biosimilars market is projected to reach USD 44.7 billion by 2026 from USD 15.6 billion in 2021, at a CAGR of 23.5% during the forecast period of 2021 to 2026

ReportLinker

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Pricing pressures and shrinking margins

COMMENTARY · GLOBALIZATION

EY: 97% of CEOs have changed their investment strategy in response to geopolitical challenges–and almost a third already halted a project

BY ANDREA GUERZONI

February 7, 2023, 3:30 AM PST

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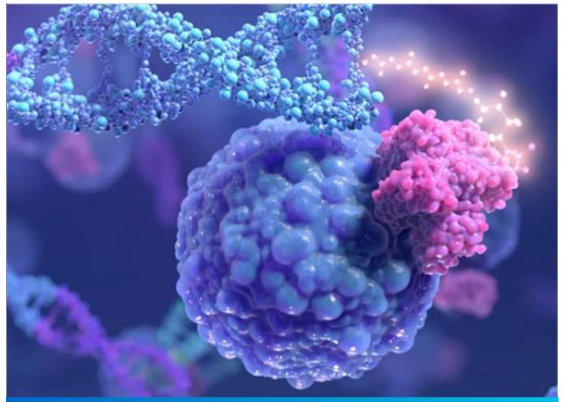
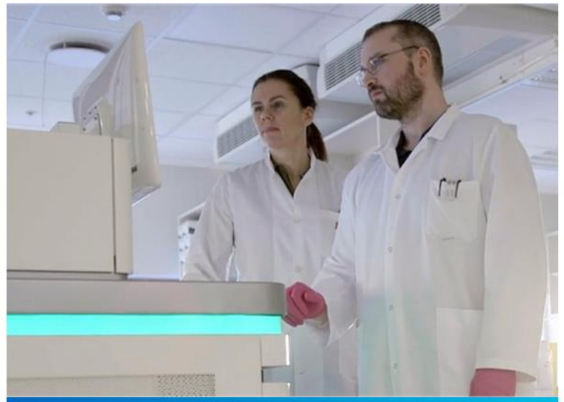
Our Science



Push the Boundaries of Biology

To discover and develop new medicines that matter for patients



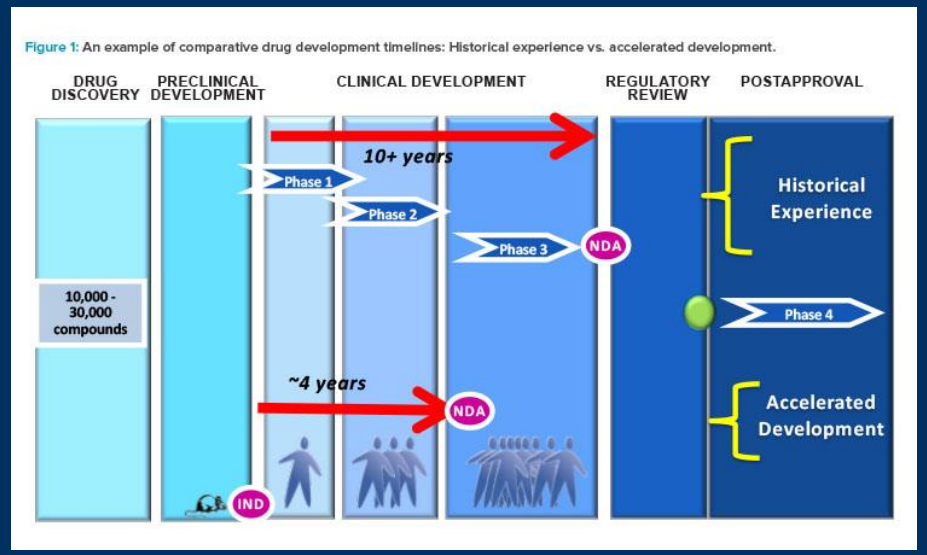
Speed to Patients

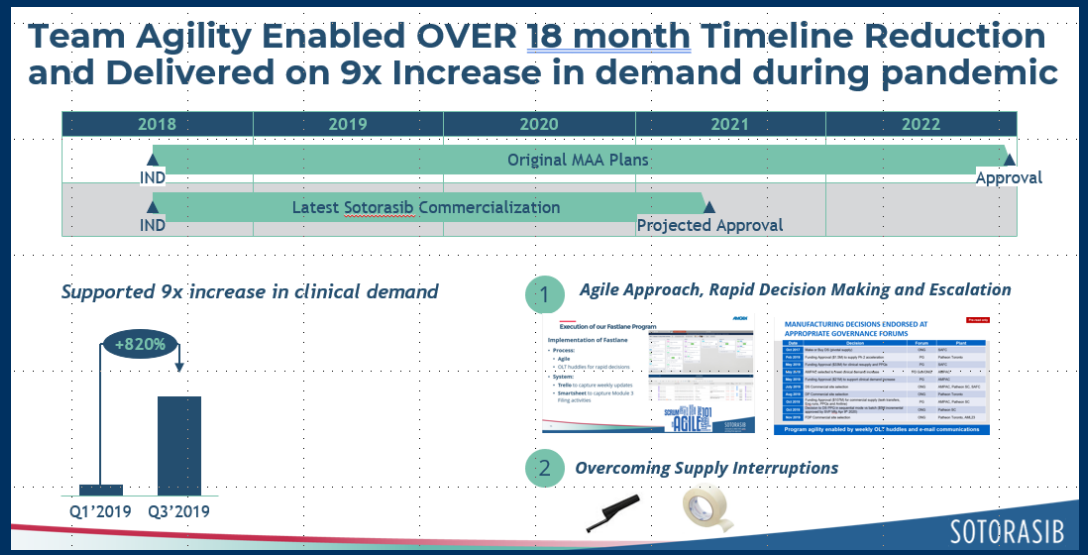
To reduce cycle times and get new medicines to patients faster than ever

For Every Patient – A Solution

To broaden access and use of our medicines for all patients

Leveraging our deep understanding of biology and human and real-world data, we are moving science faster than ever before to find new and better ways to defeat the world's toughest diseases.





2 years, 9 months

SPEED TO PATIENT

Acceleration levers are available within FDA MAPP and EMA PRIME Toolbox to support expedited product development

MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5015.13

POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Quality Assessment for Products in Expedited Programs

- **Performing certain CMC confirmatory studies post-approval**
- **Decoupling validation** of drug substance and drug product processes
- **Concurrent validation/**concurrent release approach
  - Available data supports that the process is in a state of control
- Other validation streamlining approaches e.g., **validation of certain unit ops at reduced scale** and then confirmed post approval at commercial scale
- **Alternate approaches** to stability data
- **Predictive modeling** (small molecules, not recommended for large molecules or could be justified)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2022
EMA/CHMP/BWP/QWP/IWG/694114/2019
Committee for Human Medicinal Products (CHMP)

Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

- Use of **Prior Knowledge** in science-driven, risk-based approaches
- Process Validation
  - **Concurrent**
  - **Decoupled**
  - Deferred submission of certain data (hybrid)
  - Continuous Process Verification
- '**Adapted' control strategy** with tighter controls
- **In silico** models
- Specifications using **prior knowledge**
- Launch from clinical manufacturing site
- **Stability models** (small molecule & biologicals)
- **Risk-based comparability** (biologicals)

Can we expedite CMC development beyond pandemic therapies?

The AAPS Journal (2022) 24:101
https://doi.org/10.1208/s12248-022-00751-9

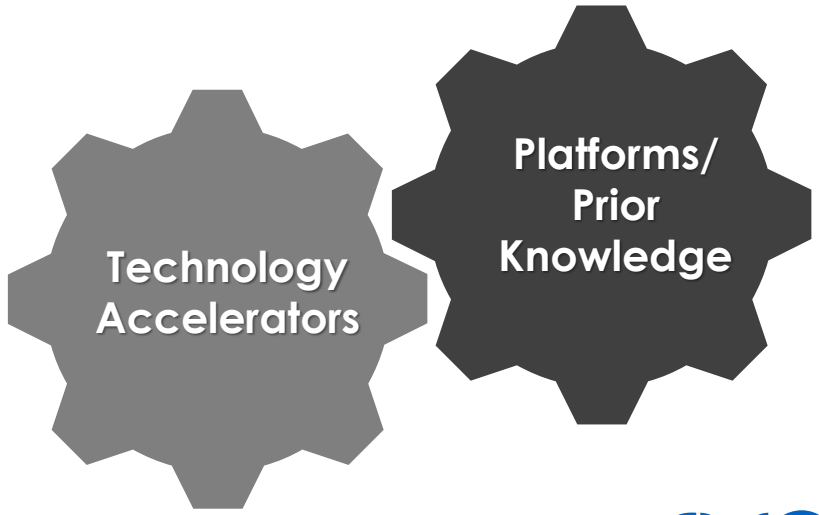
REVIEW ARTICLE

Chemistry Manufacturing and Controls Development, Industry Reflections on Manufacture, and Supply of Pandemic Therapies and Vaccines

Matthew E. Popkin[1] · Markus Goese[2] · Diane Wilkinson[3] · Stuart Finnie[4] · Talia Flanagan[5] · Cristiana Campa[6] · Alexandra Clinch[7] · Andrew Teasdale[8] · Andrew Lennard[9] · Graham Cook[10] · Ganapathy Mohan[11] · Matthew D. Osborne[12]

CMC Acceleration Levers
• Decoupled PPQ: Use of clinical DS for DP PPQ
• Submit MA prior to completion of DP PPQs
• Seek Real Time Oncology Review
• Utilize predictive modeling for stability
• Perform risk-based comparability
• Submit MA with clinical formulation/SKUs

- Several of the CMC acceleration levers that were applied for pandemic therapies can also be applicable for therapies intended for serious illness and with the potential to offer substantial improvement in clinically significant endpoint
- The biopharma industry also needs acceleration levers that can be more widely applied to all portfolio assets: solutions that are sustainable and scalable



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Platforms – depth of knowledge in a proven design space to enable confidence and predictability

Platforms are critical enablers for increasing efficiency and speed in development and manufacturing workflows

- Standardized and scalable processes
- Reduction in resources, material demand and waste
- Reduced cycle times

- A Fit-to-platform governance process
- Formulation platforms
- 1st intent manufacturing process that is aligned with network capabilities
- Industry leading and/or industry aligned approach to data packages
- Standardized container closures
- Offline capabilities to enable transferability
- A 1st intent control strategy in alignment with regulatory expectations
- Culture of continuous improvement

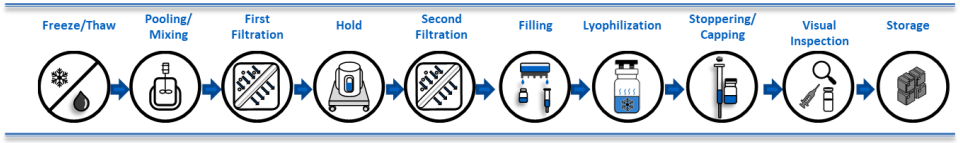
Driving Efficiency and Speed in Process Development through Optimized Attribute Testing

Example:

Impact of freeze thaw stress on drug product quality

First principle mechanistic understanding coupled with prior experience guides optimized attribute testing plan during process development studies

Attributes measured	Potential mode of attribute impact	Attribute impact based on prior data?	Is the attribute recommended for testing ?	Rationale for optimized attribute testing
pH	Cryo-concentration causing pH gradient	No	Yes	To confirm there is no pH gradient post thaw and mixing
Protein concentration	Protein concentration gradient	No	Yes	To confirm there is no protein conc. gradient post thaw and mixing
Osmolality	None	No	No	No process impact expected
Aggregation (SE-UHPLC)	Increase in HMW	**Yes**	Yes	Indicator of process stress on aggregation
HIAC	Increase in particulates	**Yes**	Yes	Indicator of process stress on subvisible particle count
Chemical degradation (peptide map)	Increased chemical degradation	No	Conditional	Test as needed (if significant degradation observed on purity)



Attributes ↓	Freeze thaw	Dilution	Mixing	BBR filtration	In-process hold	Filling	VI CRT/ light exposure	Lyophilization	Transport simulation	Stability
pH										
Protein concentration										
Osmolality										
Aggregation										
Charged variants										
Fragmentation										
Particle count										
Particle morphology										
Chemcial degradation										
Potency										
Visual appearance										
Color										
Clarity										
PS80 content										
Lyo cake appearance										
Reconstitution time										
Moisture content										
Plunger depth										
BLE										

Attribute not relevant for that stressor
No impact expected and tested
Potential impact based on 1st principle
Confirmed impact based on prior experience

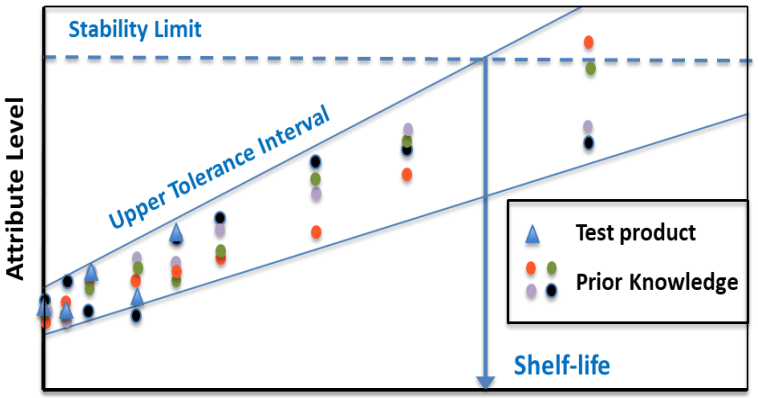
Prior experience with different processes stresses can be aggregated to build knowledge maps to guide formulation and process design

Use of prior knowledge for stability prediction can take stability off the critical path for product development

- Long term stability data can often be on critical path for product development

- Prior knowledge available from 'like molecules' can be leveraged to make stability predictions with limited dataset
  - Bayesian statistics – statistical parameters adjusted to molecule likeness
  - AI machine learning enabled models - inputs set 'likeness'

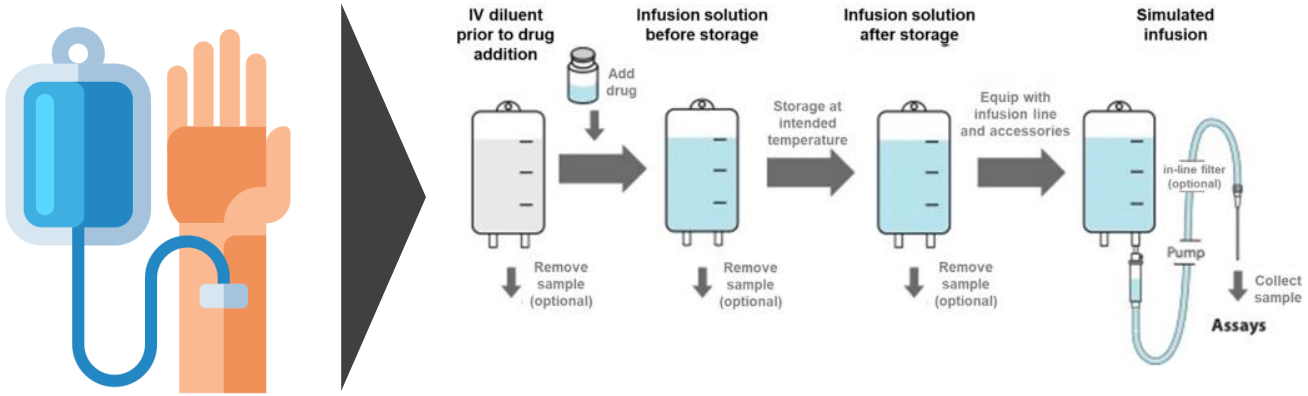
- Relies on understanding of degradation pathways and risk assessments
- Stability models do not replace long-term stability data that verify the model post-approval
- EMA toolbox incorporates use of stability models for unmet medical need
- Revision of ICH Stability guidelines are in progress to adopt science & risk-based approaches



Quality by Design— An Indispensable Approach to Accelerate Biopharmaceutical Product Development - Chapter 8 Using Prior Knowledge for Stability Modeling of Biological Therapeutic Agents to Assign Shelf Life. Andrew C. Lennard, Amgen Fuat Doymaz, Amgen Nic Angell, Amgen Jette Wypych, Amgen; 2021

Prior knowledge provides a scientific basis to extending shelf-life beyond product-specific data

Standardized approach for in-use stability assessment



Administration components	Recommended material to be tested	Additional materials, usually only tested to support commercialization
Infusion bag	PVC, PO	EVA
Syringe	PP, PC[1]	N/A
Administration set (giving set, infusion line)	PVC, PE	PUR, PBD
In-line/add-on filter	0.2 or 0.22 μm PES	PA/Nylon, PS
Access Device (cannula, short peripheral venous access devices (PVADs)	PUR	FEP, PTFE, ETFE
Injection needle (with gauge suitable for route of administration)	SS	N/A
Infusion aid (3-way stopcock)	PC	N/A

Prior experience can help reduce the dimensionality of the design space to be characterized

- Material of construction of admin components
- Diluents/admixtures
- In-line filters
- Protein concentration
- Temperature, duration of holds and infusion, simulated handling
- Infusion rates
- Attributes to be tested and acceptance criteria

Journal of Pharmaceutical Sciences 112 (2023) 2332–2346

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

Current Industry Best Practice on in-use Stability and Compatibility Studies for Biological Products

Check for updates

Markus Blümel[1,a,*], Jing Liu[1,b,*], Isabella de Jong[c], Sarah Weiser[d], Jonas Fast[e], Jennifer Litowski[f], Melissa Shuman[g], Shyam B. Mehta[h], Leanne Amery[i], David Cheng Thiam Tan[j], Feng Jia[k], Dushyant Shekhawat[l], Camille Dagallier[m], Mina Emamzadeh[i], Annette Medina[n], Camilla Santos[o], Florian Gasser[p], Christian Urban[q]

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

A consolidated industry approach on design of in-use stability studies that encompass the design space parameters along with quality standards and regulatory requirements to enable clinical and commercial stage development

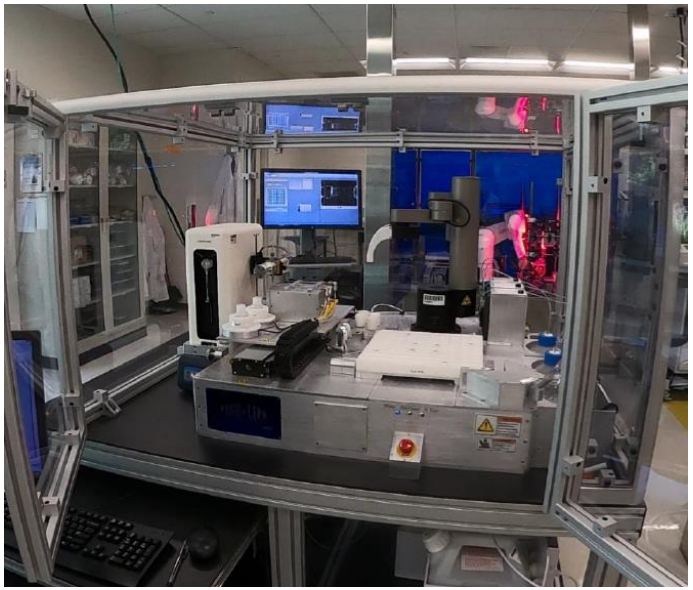
PDA Journal of Pharmaceutical Science and Technology

Best Practices for Microbial Challenge In–use Studies to Evaluate the Microbial Growth Potential of Parenteral Biological Products; Industry and Regulatory Considerations

Camellia Zamiri, Danielle L. Leiske, Patricia F. Hughes, et al.

PDA Journal of Pharmaceutical Science and Technology **2023**,
Access the most recent version at doi:10.5731/pdajpst.2022.012806

Automation is another key enabler for efficiency and consistency in development workflows



Automated HIAC for subvisible particle enumeration

Automated Karl-Fisher for moisture measurements

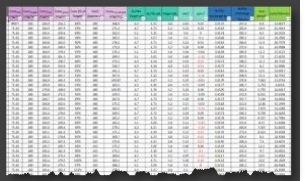
Work plan visualization

Formulation and SKU databases

Structured report authoring

Fit to platform visualization

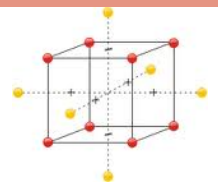
Use of AI/Gen AI

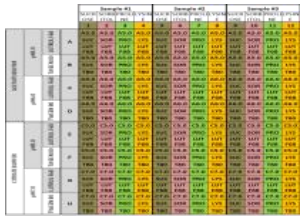


Automated visualization: Structured databases enabling rapid visualization and data insights

Automation coupled with miniaturization and high throughput can further accelerate development workflows

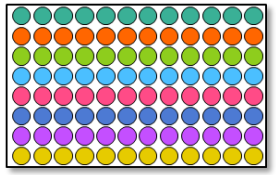
Statistical Design of Experiments





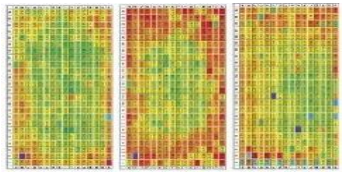
Automated and Miniaturized High Throughput Formulation Development

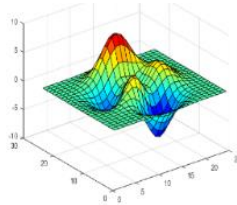
Liquid Handler and Plate-Based Buffer Exchange System



Up to 96 New Formulations Per Plate

Actionable Data and Decision Making





Journal of Pharmaceutical Sciences 110 (2021) 1130-1141

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journal homepage: www.jpharmsci.org

Pharmaceutical Biotechnology

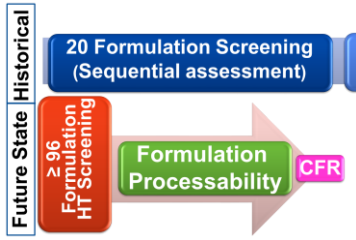
Application of a High Throughput and Automated Workflow to Therapeutic Protein Formulation Development

Cindy D. Ren*, Wei Qi, Emily A. Wyatt, Jeffrey Yeary, Kimberly Westland, Michael Berke, Nitin Rathore

Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, California 91320

SPEED

Accelerating development via automated HT capabilities and agile workflows :



4-5 months head-start

EFFICIENCY

Utilizing **automation** to drive reduction in FTE hours on routine manual operations

> 65% reduction in FTE hours for **particle characterization**

QUALITY

Improve consistency and quality of data using automated methods

Enable broad design (**5X**) space characterization for robust formulation design

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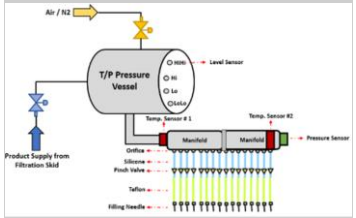
Offline capabilities have proven to be key enablers for speed to clinic and speed to market

Predictive models reduce need for experimentation by applying first principles understanding and/or prior knowledge towards process design and tech transfer

Lyophilization

Models for lyo cycle development and transfer

Filling



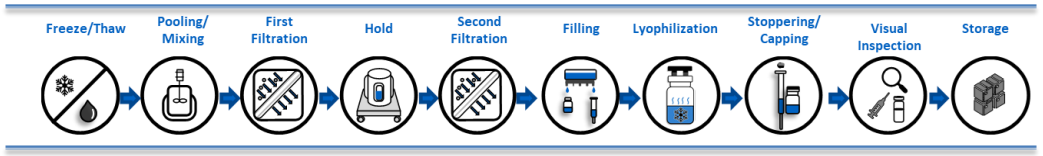
Models for fill recipe development and transfer

Plunger Placement

Models for plunger placement recipe

Use of machine learning is making models more powerful and robust in leveraging prior knowledge for designing predictive solutions

Lab and pilot scale systems minimize the need for manufacturing scale development while offering experimental verification of process performance



- Product impact assessment
- Filter sizing
- Impact of hold times
- **Filling recipe development**
- Lyo cycle development


Journal of Pharmaceutical Sciences 112 (2023) 954–962

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journal homepage: www.jpharmsci.org

Pharmaceutical Biotechnology

Investigating and Addressing Challenges Associated with Filling Protein Drug Products

Neha Pardeshi, Dan Marsiglio, Vikashni Padmakumar, Joe Bernacki, Nitin Rathore*

Drug Product Technologies, Amgen, Thousand Oaks, CA 91320, USA

Offline capabilities are becoming increasingly sophisticated and offer a less resource, time and material intensive approach for process design

Reduction in tech-transfer cycle times can reduce at-risk investments while ensuring right first-time execution

Agility is the best antidote to uncertainty

- Commitment to the concept of standardization and platforms
- Simplification of business processes to eliminate waste and ensure lean execution
- Modularization of complex and large work packages to enable agility in off-platform development
- Continuous improvement mindset coupled with pursuit of transformative solutions
- Culture of innovation and excellence
- Investment in training and development of Workforce

AMGEN

Agility is a strategic focus area for Amgen Operations

Acknowledgements

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- Cindy Ren
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- Monica Goss
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- Chris Collier