Patient-Centric Innovation to Modernize the Development and Manufacture of Biologics

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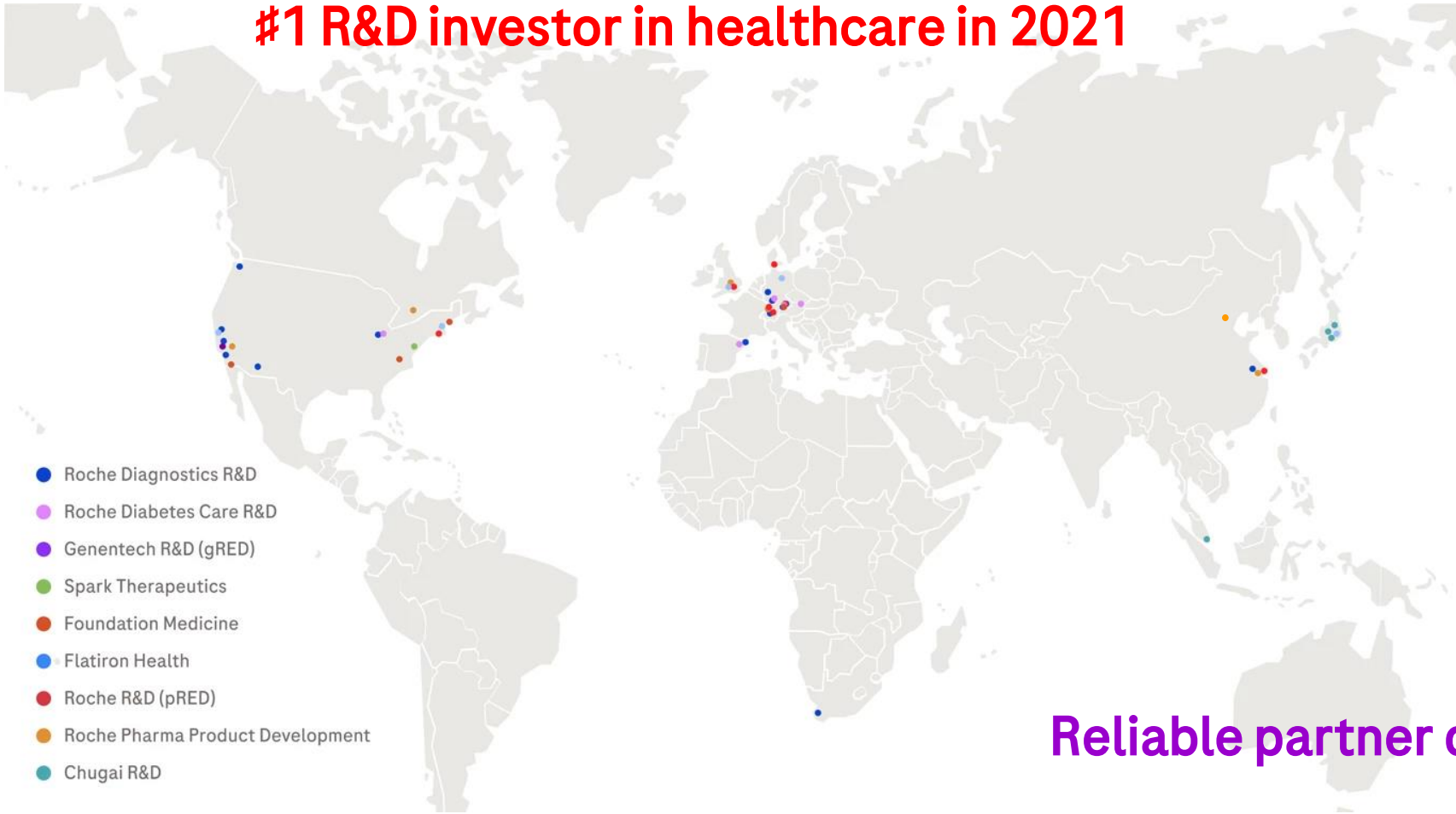
Genentech, a member of the Roche Group

Roche - a global pioneer in pharmaceuticals and diagnostics

#1 R&D investor in healthcare in 2021



>100,000 dedicated employees over 150 countries

CHF 13.7 billion invested in R&D in 2021

17 countries with Roche innovation centers

16.4 Million people treated with our medicines in 2021

Reliable partner during COVID-19 pandemic

"Put Patient First"

Roche Pharma Vision 2030: *3-5 times more* patient benefit at ***50% less cost* to society**

"Follow the science"

End to end innovation portfolio to deliver patients' needs

Biologics

Examples of current innovation efforts

CHO Cell Line Engineering

Advanced Drug Delivery (ocular, SC, brain)

RTRT (Real Time Release Testing)

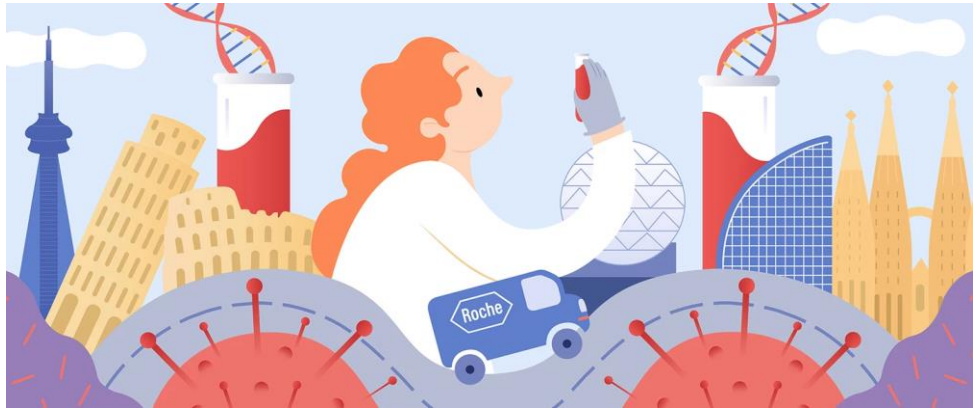
NGS (next generation sequencing)

Single Use Technology

Modular Biomanufacturing

Rapid Sterility (Celsis)

In silico Modeling



Multi-Attribute Methods (MAM by LC-MS and MARS)

Rapid Micro (Growth Direct)

Smart Device and Packaging

Novel excipients

Process Intensification

Process Analytical Technology (PAT)

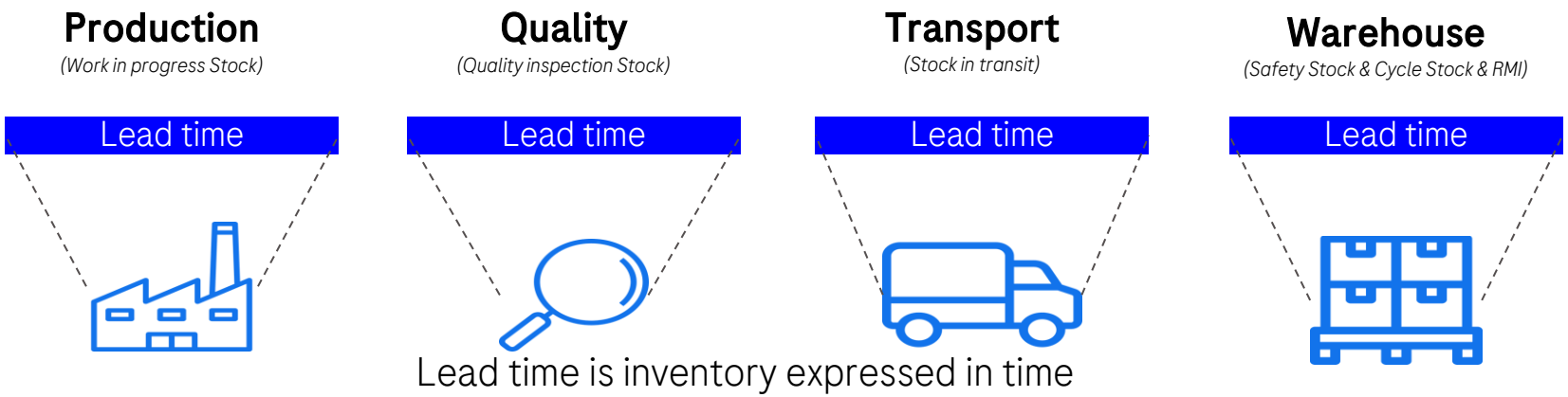
Lyophilization with Controlled Ice Nucleation

Robotics and Automation

Data & Digital Backbone

Disruptive changes needed to reduce lead time

Lead time: 92% is product waiting time (released and unreleased inventory)



Lead time is inventory expressed in time

Our North Star:

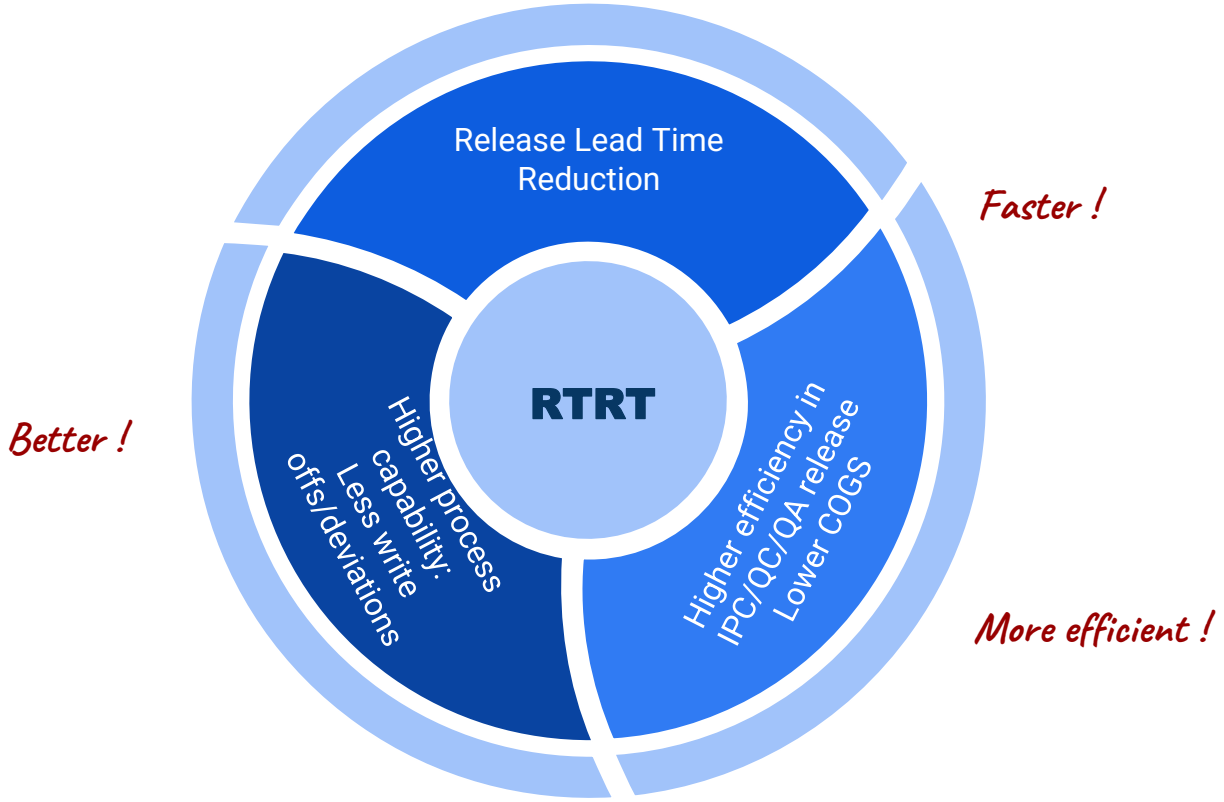
Product (DS, DP or FP) can be shipped to patients as soon as the "production" is completed <u>without waiting periods</u> for quality testing and release.

Real Time Release Testing (RTRT)

Definitions:

RTRT is a system of release tests or methods that gives assurance that the product is of intended quality, based on the information collected during the manufacturing process, through product knowledge and on process understanding and control. (EMA RTRT guidance)

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (ICH Q8 (R)).

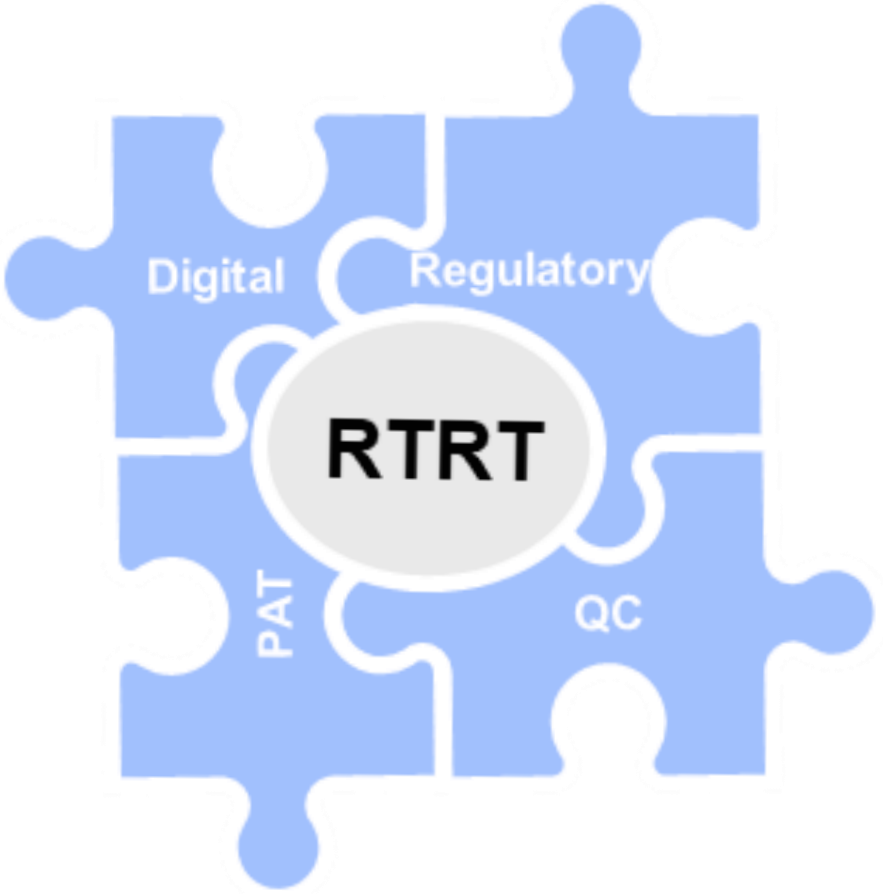


Patient centric: ensure patient safety, product efficacy and increase treatment convenience

Main elements of a RTRT control strategy

- Movement of release testing points upstream in the process
- Replacement of conventional QC method(s) with rapid or more efficient analytical method(s)
  - **Multi-attribute methods**
- Replacement of end product release testing with in-process controls
- Parametric release, i.e. combination of process control and (IPC/QC) analytic results supported by predictive modeling tools (e.g. MVDA)

Building blocks



Multi-Attribute Methods: Why Do We Need Them?

Current Large Molecule Control System

Category	Test Name	PQA
Appearance	Clarity, Opalescence and Color	
Formulation Tests	pH	
	Osmolality	
	HPLC-ELSD	Surfactant concentration
	SoloVPE	Protein Concentration
	HPLC	Anti-oxidant Concentration
Identity	Lys-C Map	Protein ID
Purity	SEC	HMWF
		Main Peak
	IEC/iCIEF	Acidic Region
		Main Peak
	CE-SDS (NR)	Sum of LMWF
	CE-SDS (R)	NGHC
	HILIC-Glycan	Afucosylation
		Galactose
		High Mannose
	HPLC	Oxidation
Impurity	HCP	
	LAL	
	Bioburden	
Bioactivity	Potency	

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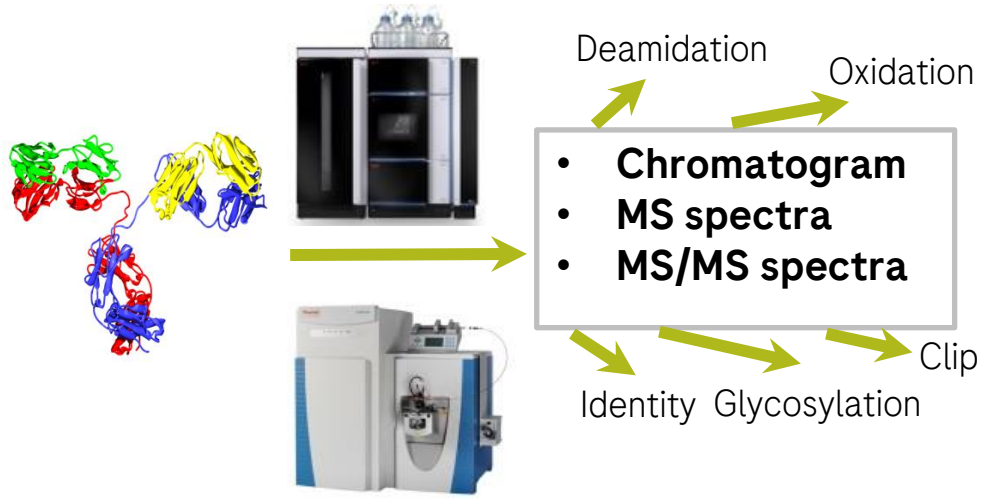
Complex and Cumbersome

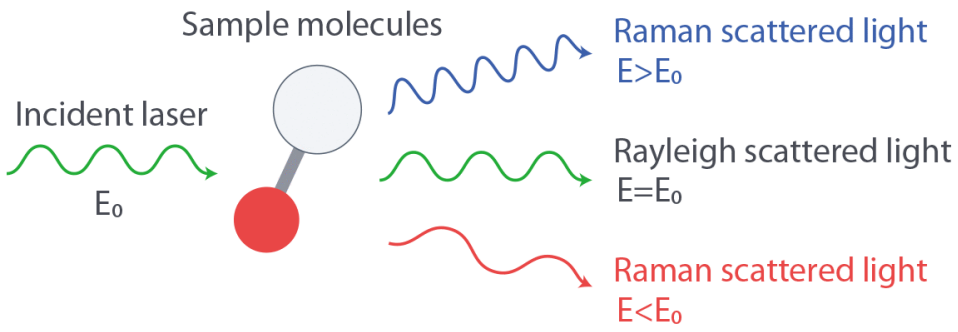
Solution

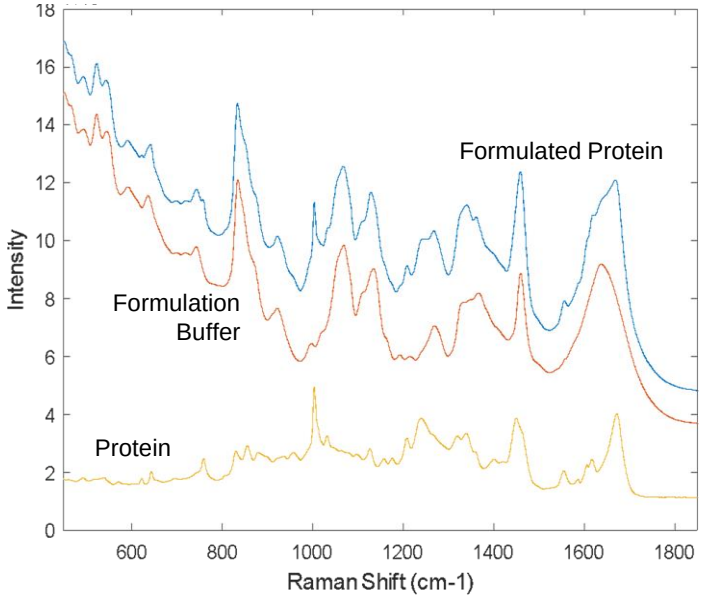
Replace current/conventional assays with Multi-Attribute Methods!



More efficient and informative

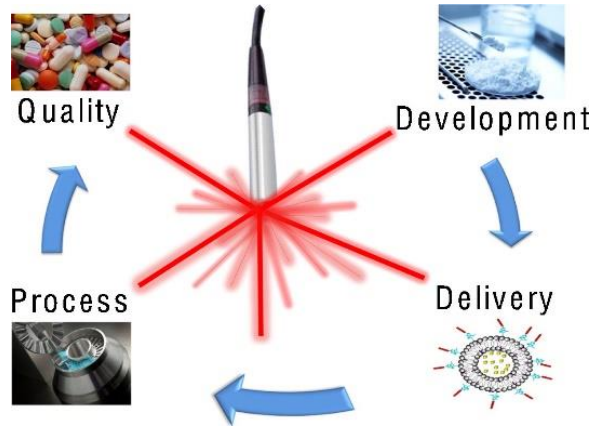
Multi-Attribute Raman Spectroscopy (MARS)



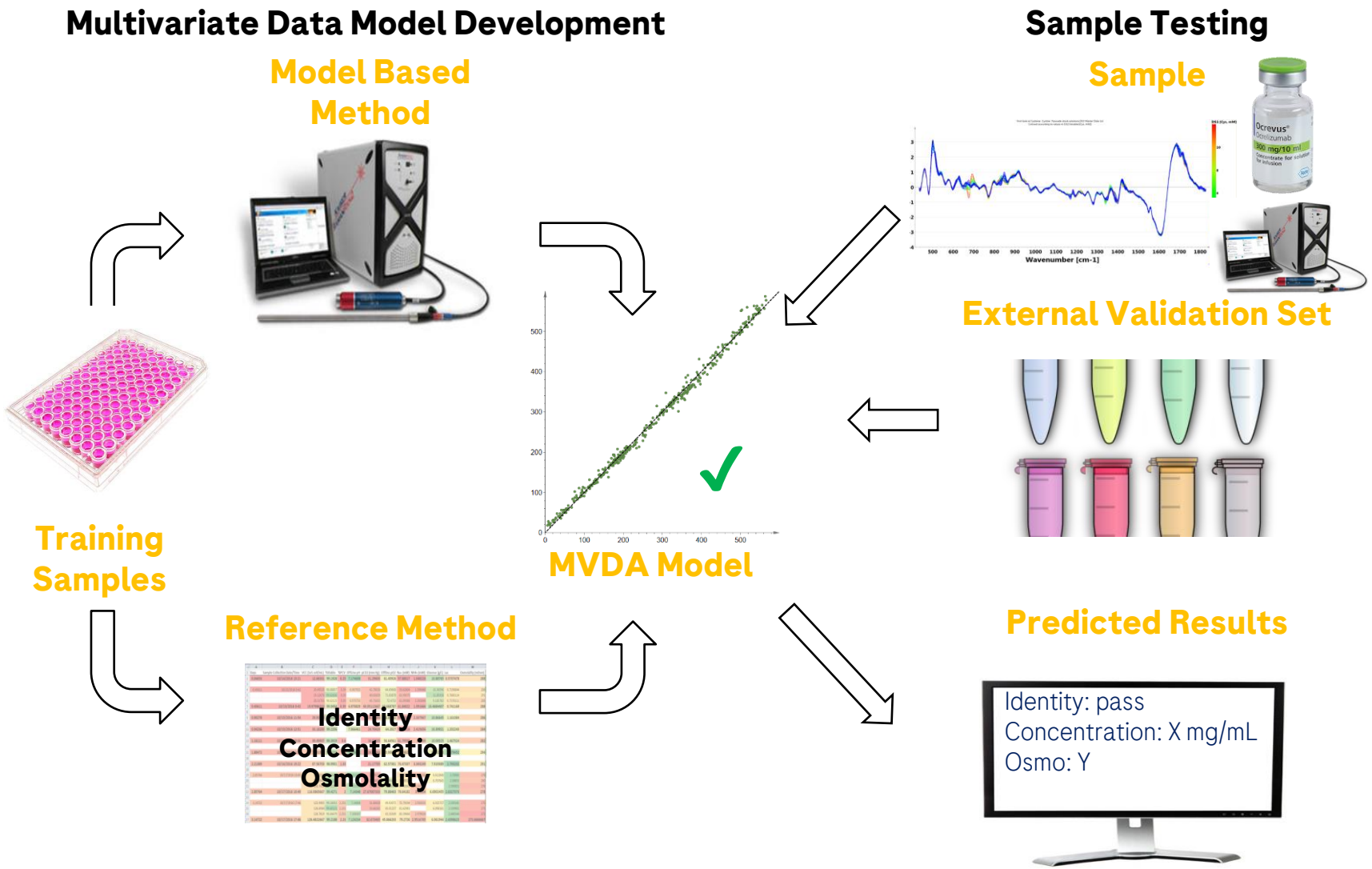


Why do we choose Raman?

- Potential multi-attribute method because the spectra contains all Raman active chemical bond information
- Non-destructive analysis with no sample preparation
- Fast analysis time and immediate data report with pre-built model
- Less water interference comparing with other vibration spectroscopic methods like IR.
- Easy integration into a process as a PAT/RTRT tool



Multi-Attribute Raman Spectroscopy (MARS)



MARS for Quantifying Certain Formulation PQAs

Technical Feasibility Demonstrated

Multi-attribute Raman spectroscopy (MARS) for monitoring product quality attributes in formulated monoclonal antibody therapeutics

Bingchuan Wei, Nicholas Woon, Lu Dai, Raphael Fish, Michelle Tai, Winode Handagama, ...show all

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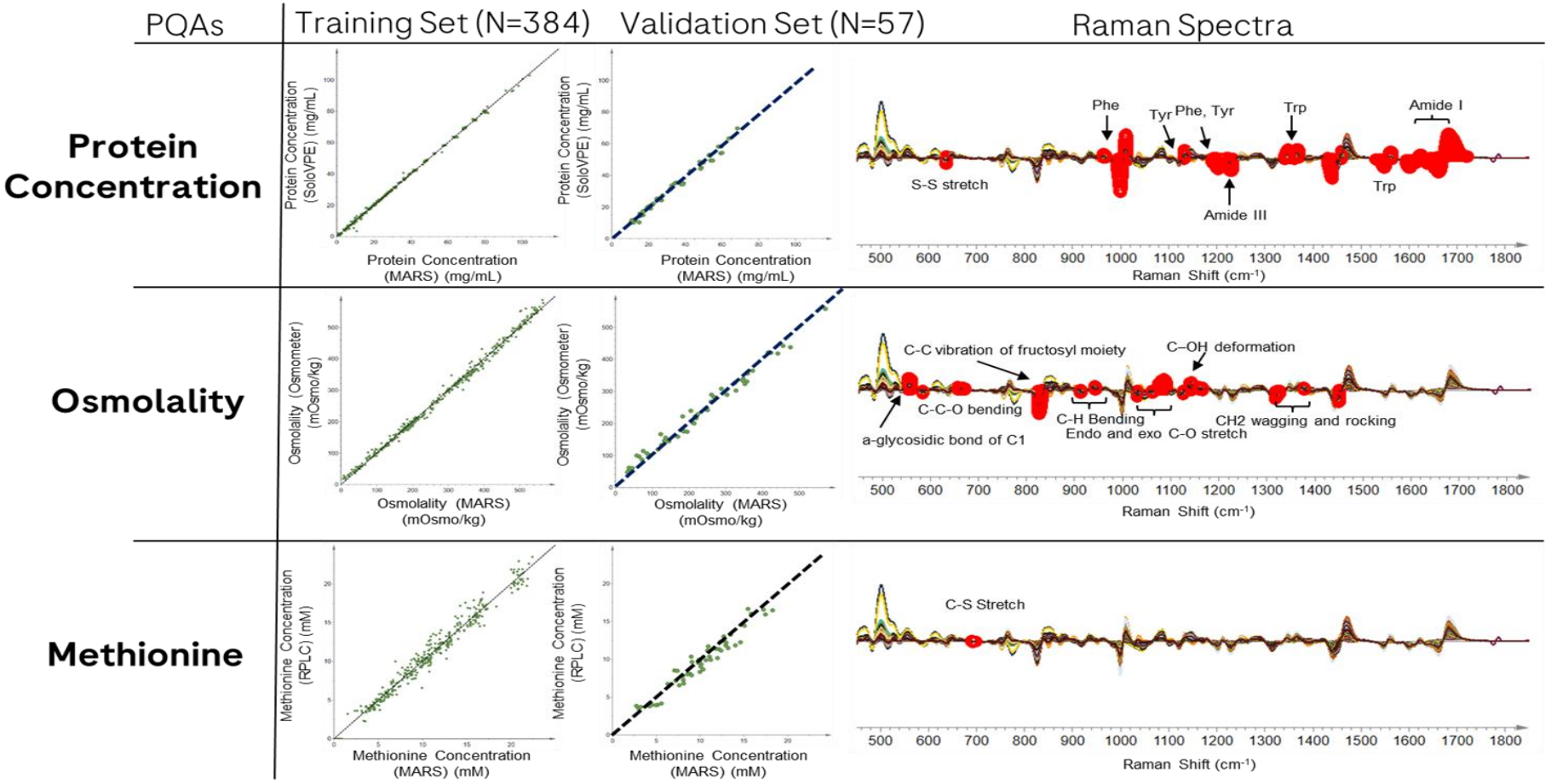
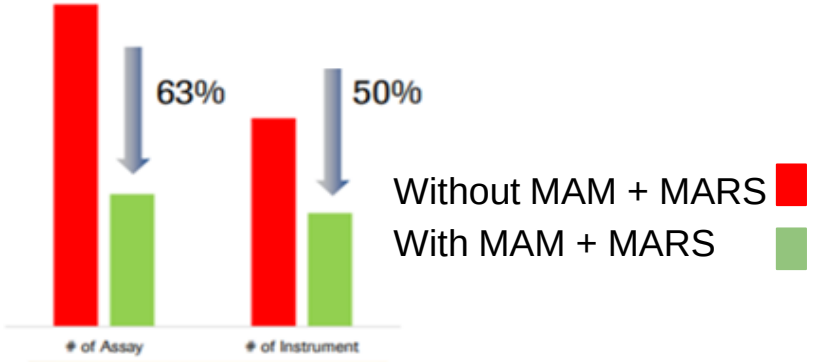


- **MARS** is proposed as a **MAM** to measure and characterize multiple CQAs of protein therapeutics **in a single spectrum scan**
- Productive discussions with FDA CDER Emerging Technology Team (ETT) and EMA Innovation Task Force (ITF)

Innovative analytical technology

Maximize Benefit by Combining MAM by LC-MS and MARS

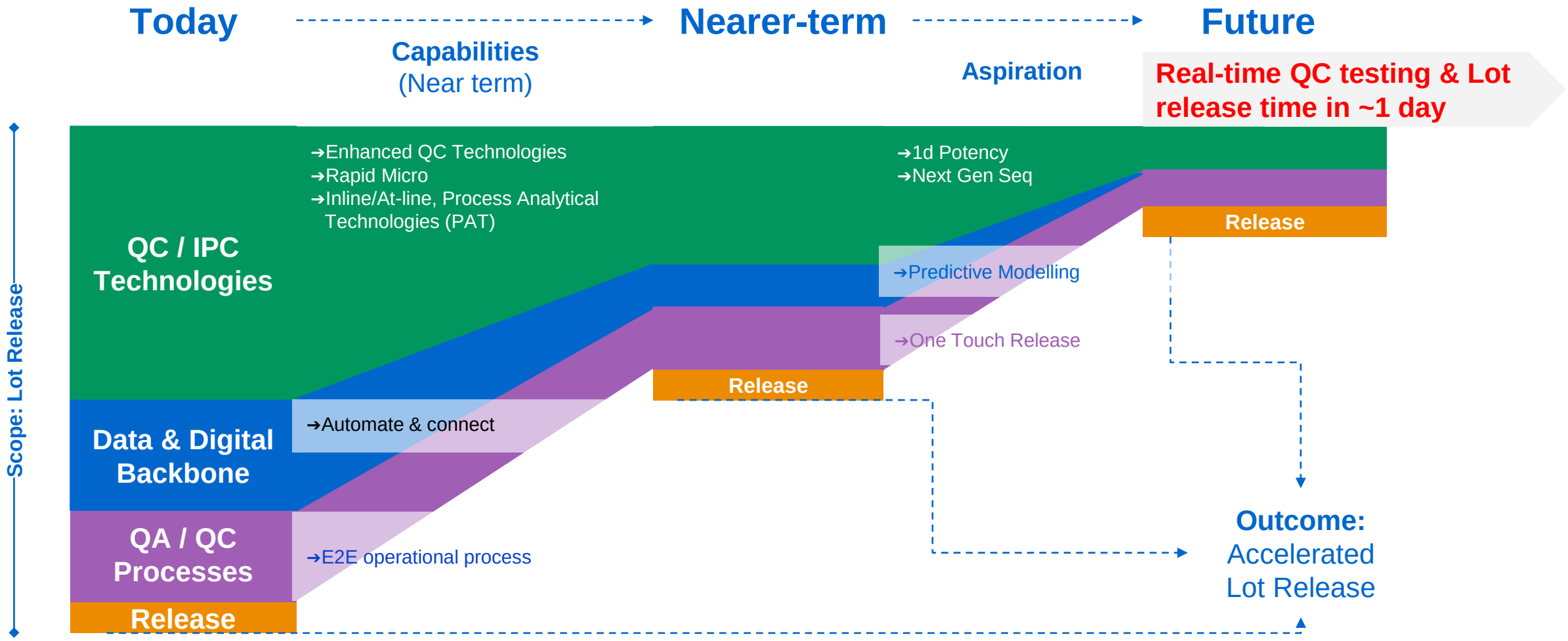
Category	Quality Attribute	Current Methods	Potential Future Control System with Multi-Attribute Methods
Appearance	Clarity, Opalescence and Color	COC	COC
Formulation Tests	pH	pH meter	MARS
	Osmolality	Osmometer	
	Surfactant concentration	HPLC-ELSD	
	Protein Concentration	SoloVPE	
	Anti-oxidant Concentration	HPLC	
Identity	Protein ID	Peptide Map	MAM or MARS
Purity	HMWF	SEC	SEC
	Main Peak (Size)		
	Acidic Region	IEC/iCIEF	MAM
	Main Peak (Charge)		
	Basic Region		
	Sum of LMWF	CE-SDS (NR)	
	NGHC	CE-SDS (R)	
	Afucosylation	HILIC-Glycan	
	Galactose		
	High Mannose		
	Oxidation	HPLC	
Impurity	HCP	ELISA	ELISA
	Endotoxin	LAL	rFc
	Bioburden	Membrane Filtering	Membrane Filtering
Bioactivity	Potency	ELISA & cell-based assay	SPR & cell-based assay



63% reduction in the number of assays
50% reduction in instrument fleet

Modernized testing strategy!

Where we are, where we want to be and what capabilities we need



Potential applications of in silico models across the product lifecycle

Computational modeling for biomolecule design

Formulation selection

CQA classification

Control strategy development

Process monitoring and predictive control

Predictive stability

Process design and validation

Developability Assessment

Scale up and tech transfer

Early device development

Fully automated data analysis

COGs

Facility design

Supply chain management

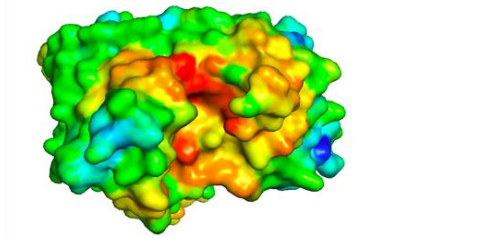
Benefits:

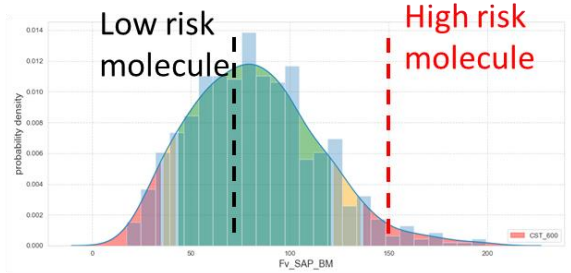
- **Accelerate end-to-end CMC development and tech transfer to GMP facility**
- **Increase process and product knowledge and improve process robustness**
- **Reduce experimentation and enables more automation leading to resource savings**

Example of current In-silico modeling efforts

In-silico Developability Assessment

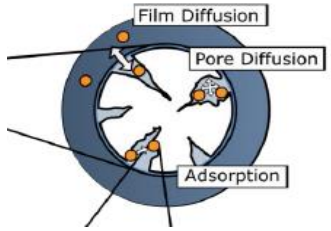
automated assessment successfully captures solubility issue

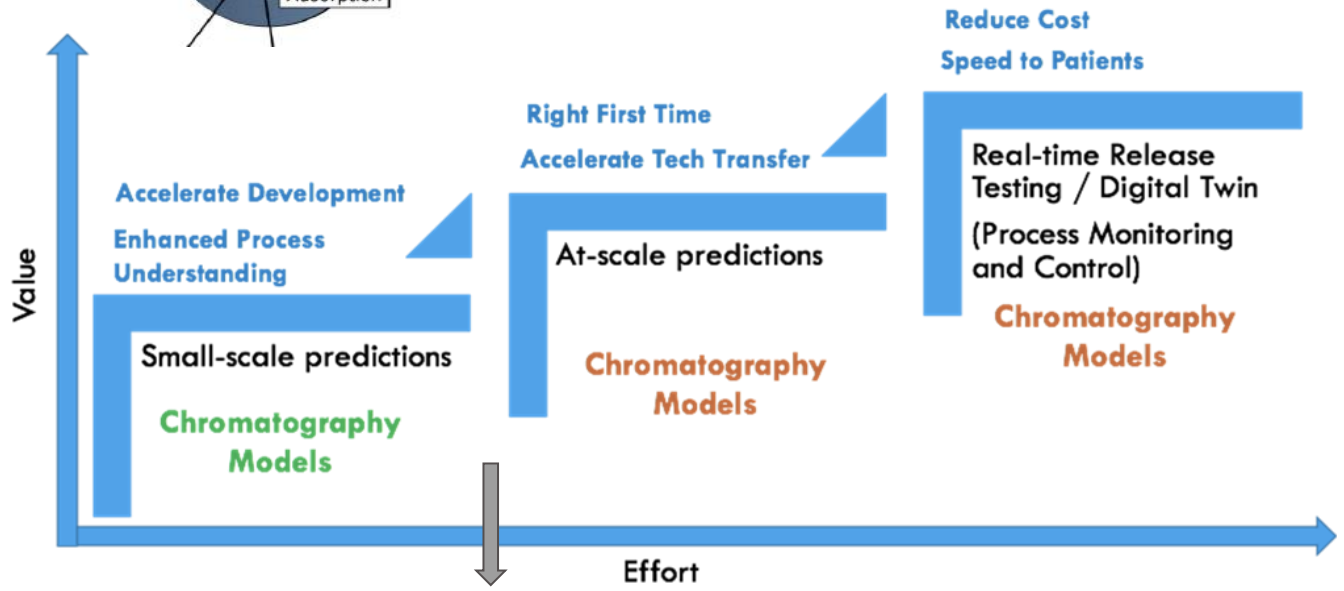


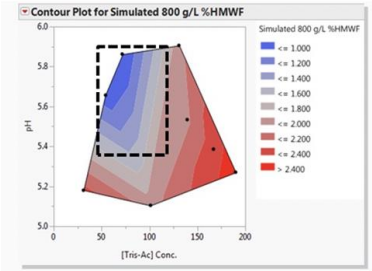


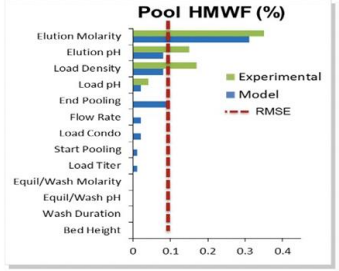
Automated Molecular Dynamics (MD)-based workflow and infrastructure that can be used to predict the developability of molecules with respect to physical stability

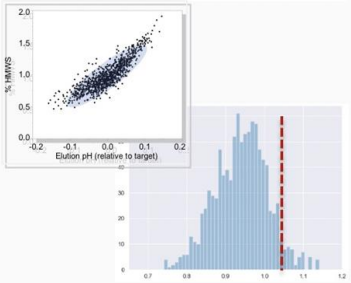
Mechanistic Chromatography Modeling









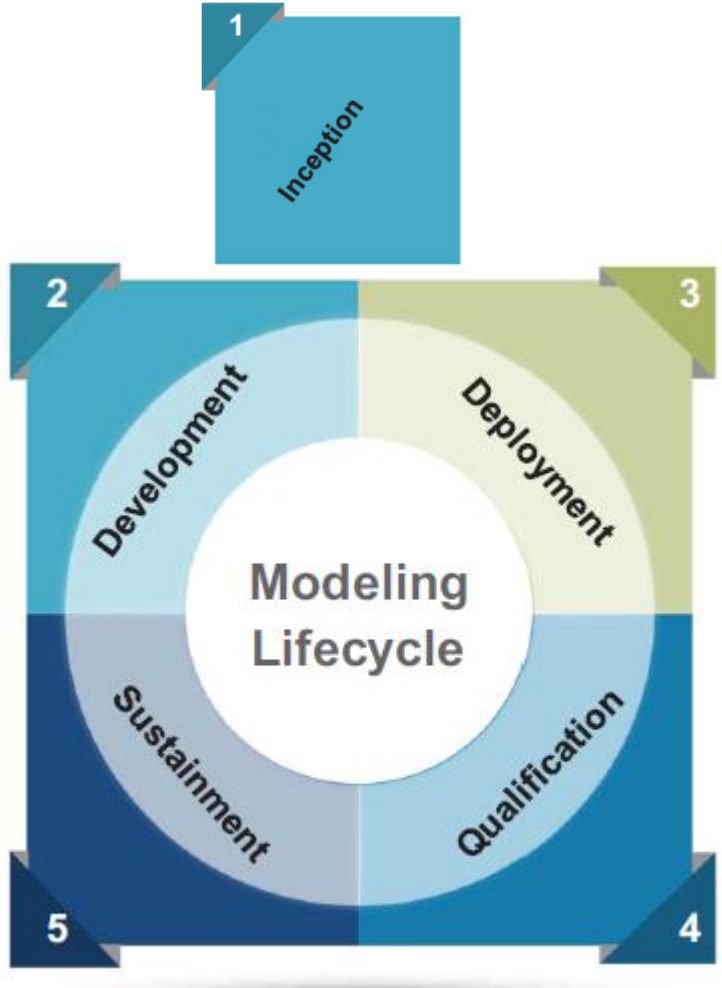


In-silico modeling for commercial process support

Launch → Stabilize → Optimize

Potential benefits include

- In silico scale-up/tech transfer to ensure fast and successful (Right First Time) launch
- Rapid assessment of raw material variability impact on process performance
- Predicting and preventing process anomalies before they occur
- Fast Root Cause Analysis
- When combined with PAT, could enable RTRT and adaptive process control

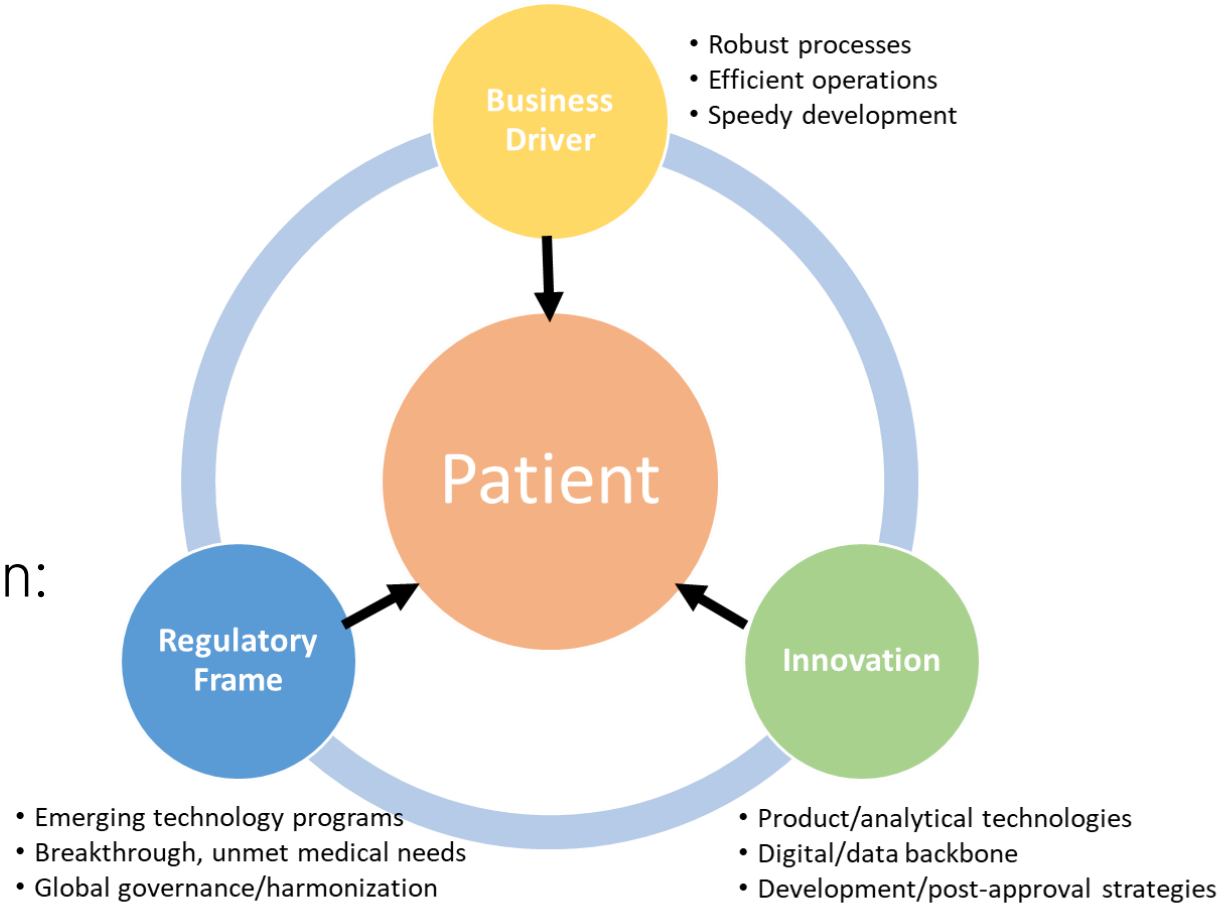


Roush, David, et al. *Biotechnology and Bioengineering* 117.12 (2020): 3986-4000.

Require active lifecycle management!

Summary

- Keep the patient's interests at the decision center
- Innovate process, product and analytical technologies with digital backbone to modernize the development and manufacture of protein biologics
- Benefited from healthy authority interaction: FDA Emerging Technology Team (ETT) and EMA Innovation Task Force (ITF)



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Tongtong Wang

....many more

Thank you for your interest

Doing now what patients need next