May 29-30| Aaron B. Cowley

A Trailblazing Digital Approach Coupled with PAT-Enabled Rapid Manufacturing from MIT and ReciBiopharm (Case Study No. 01 xRNA)

AGENDA

01 WHO WE ARE
A Leading CDMO | Capabilities

02 OUR VISION AND WHAT WE HAVE/ARE BUILDING
Integrated & Intelligent Manufacturing | Partnership with MIT

03 RESULTS/OUTCOME
Leading PAT in xRNA manufacturing | Condensed Timelines

04 ENABLING TECHNOLOGIES AND VALUE TO THE INDUSTRY
Products: PAT-SKID & CP2 | For xRNA and Beyond

A GLOBAL CDMO

5,200+
Employees worldwide at 3/09/24

100+
Supplying over one hundred markets around the world

18
Development and manufacturing facilities in Europe, Israel, USA and India

1,000+
Every minute over one thousand people use one of our products

€ 0.8 bn
Net sales (FY23)

400+
Customers

ReciBio Pharm

STRONG EXPERIENCE IN NUCLEIC ACIDS ACROSS MODALITIES AND CUSTOMERS

Expertise

Therapeutic areas	Gene Editing, Rare Disease, Oncology
Modalities	mRNA, circRNA, saRNA, siRNA, sgRNA
Encapsulation Technologies	LNPs & PNPs

Customers

15 Nucleic Acid Customers

6 Programs in the Clinic

Manufacturing

26 Total Batches

29 Batches Scheduled*

17 Drug Products Made

15 Drug Products Scheduled

**Includes 4 PPQ runs for an mRNA*

ReciBio Pharm

OUR VISION FOR MEETING INDUSTRY'S NEEDS

RBP IS DRIVING NEXT-GENERATION RNA BIOMANUFACTURING WITH MIT THROUGH FDA CBER'S LARGEST GRANT

CORE PROJECT AMBITIONS

Increase **Speed** to the Patient

Continuous & Integrated production

Compatibility with Multiple xRNA Modalities and LNP Formulation

Scalability from bench top to pandemic scale

Flexible for capability swapping to next-gen technology

CORE PROJECT AMBITIONS

- Grant spearheaded by CBER at FDA
- $82M over three years awarded to MIT
- $62M sub-awarded to ReciBioPharm (2023)
- RBP deliverables focused on industry use

OUTPUT

- cGMP manufacturing platform capable of 40g/day
- Digital PD simulator
- Process Analytics with predictive modeling, machine-to-machine communication, Real-Time Release
- Alignment with ICH Q13 guidance

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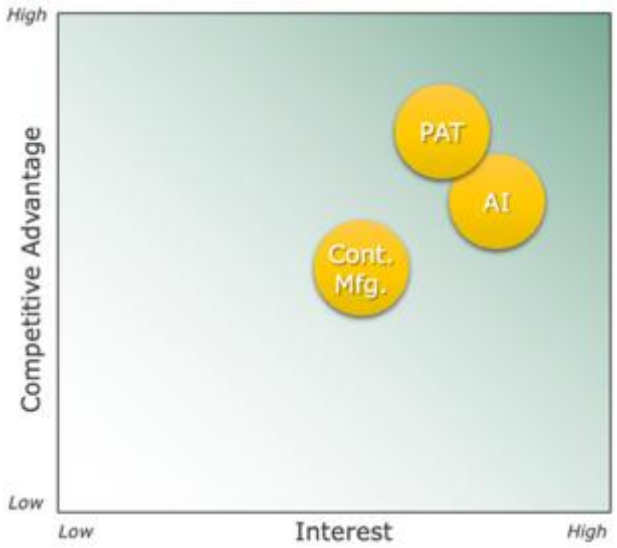
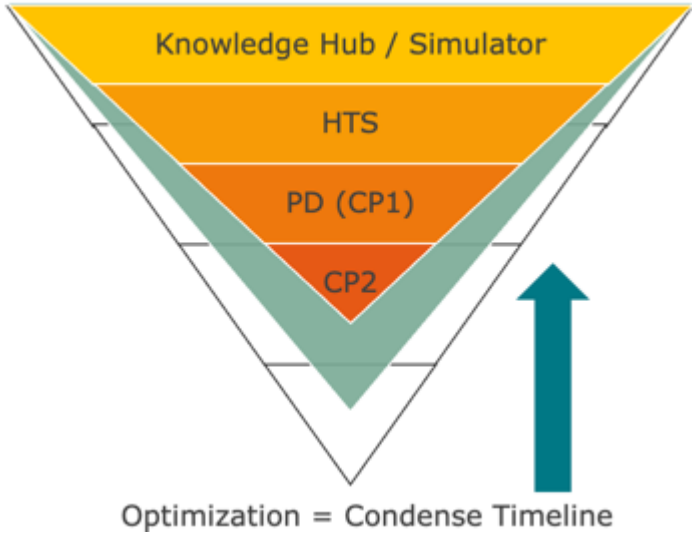
IDENTIFIED GAPS IN MARKET, TECHNOLOGY AND WORKFLOWS

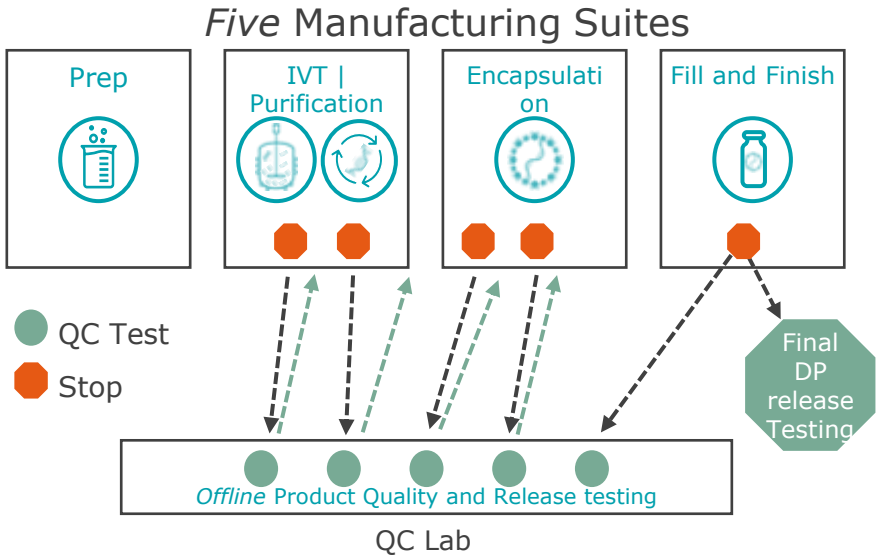
VOC Data



Length & Cost of a Program



Unecessary Inefficiences



- "PAT has utility as both a **service and product**"
- "We spend a lot of time waiting for QC results, so **in-line QC would be very exciting**"
- "It is **attractive that you can largely automate everything**, facilitating quality by design"
- Experts are willing to **pay a premium for PSPA (ML/AI models and control) + PAT additions**
- "PAT would be helpful since it creates value everywhere – **it makes things cheaper**"

A NEW APPROACH TO RNA MANUFACTURING IS CRITICAL TO ENHANCE PATIENT'S LIVES AND EXPAND THE REACH OF RNA THERAPIES

Partners

MIT

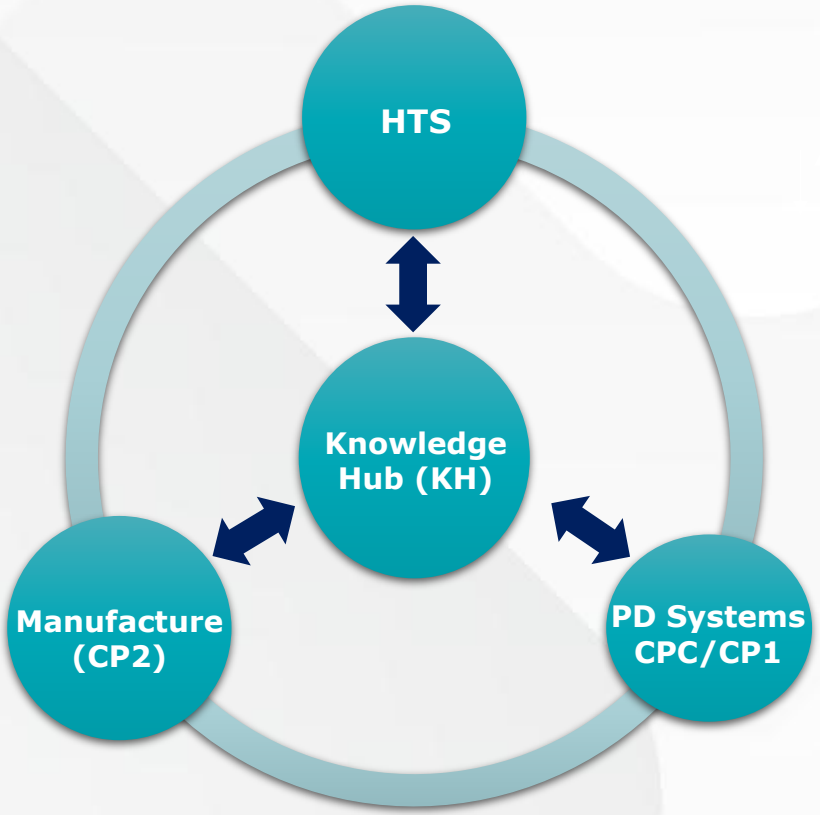
PennState

Rensselaer

FDA

ReciBioPharm's Approach to industry's needs

Digital PD and HTS/CPC	Development times drop from 6-9 months to <1 month
Integrated Manufacturing	Manufacturing times drop from months/weeks to days
Process Analytical Technologies	Real time QC removes CQA-based gating
Machine Learning Knowledge Hub / Simulator	Predictive control



The flexibility, speed, and accuracy of this platform will enable access to advanced therapeutics, reduce cost, and bring speed to vaccines in infectious disease outbreaks

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HTS PLATFORM – xRNA DRUG SUBSTANCE | SOLUTION FOR TIGHTER CONTROL AND PREDICTED OUTCOMES

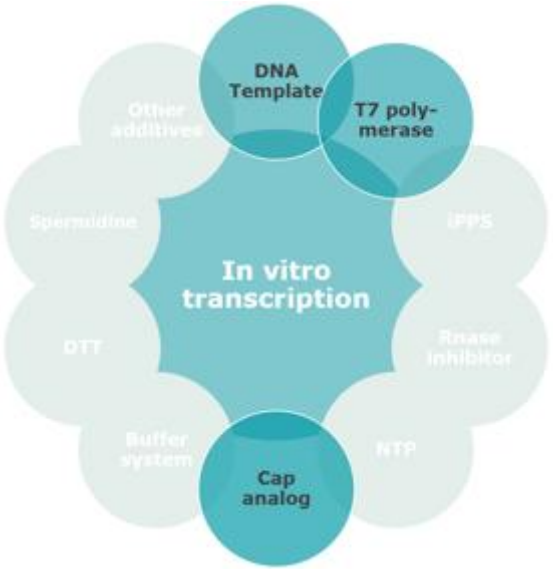
DNA Template
- Cell-free synthetic
- Plasmid

mRNA production
- IVT + purification
  - T7 library + CAP library
- Format
  - 96-well plate
  - Liquid handler + Tecan A200

Analytics
- Yields
- Purity
- dsRNA
- In vitro assay

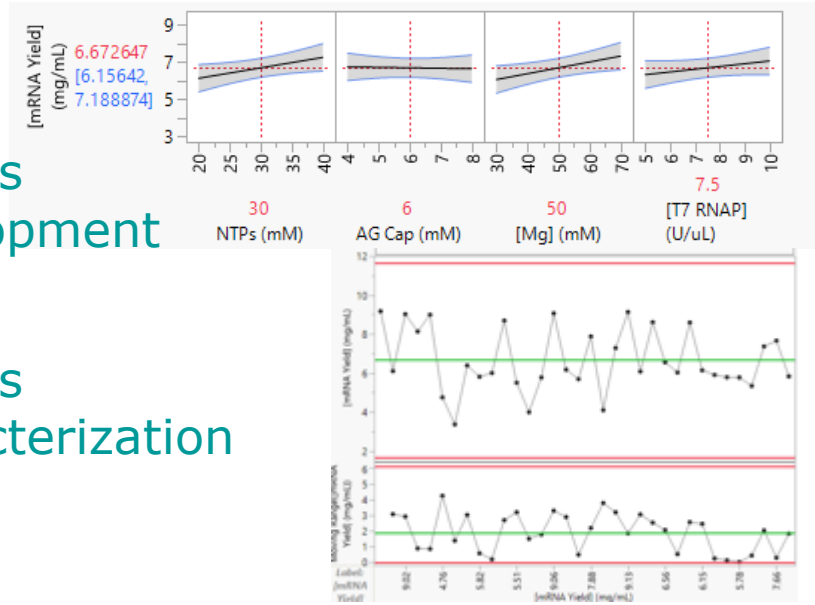
OUTPUTS

Knowledge library of key raw materials



Process Development

Process Characterization



Final database

Knowledge Hub

Simulator

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RNA PRODUCTION SYSTEMS (CPC, CP1 AND CP2): PAT IN ALL LINES

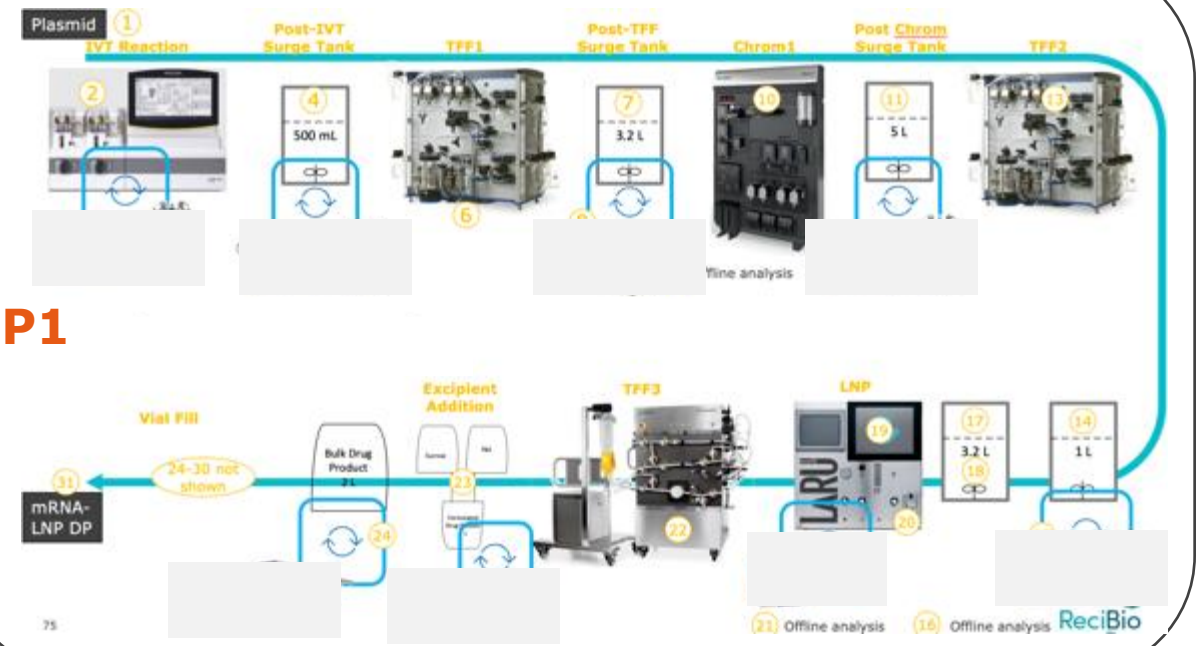
CPC

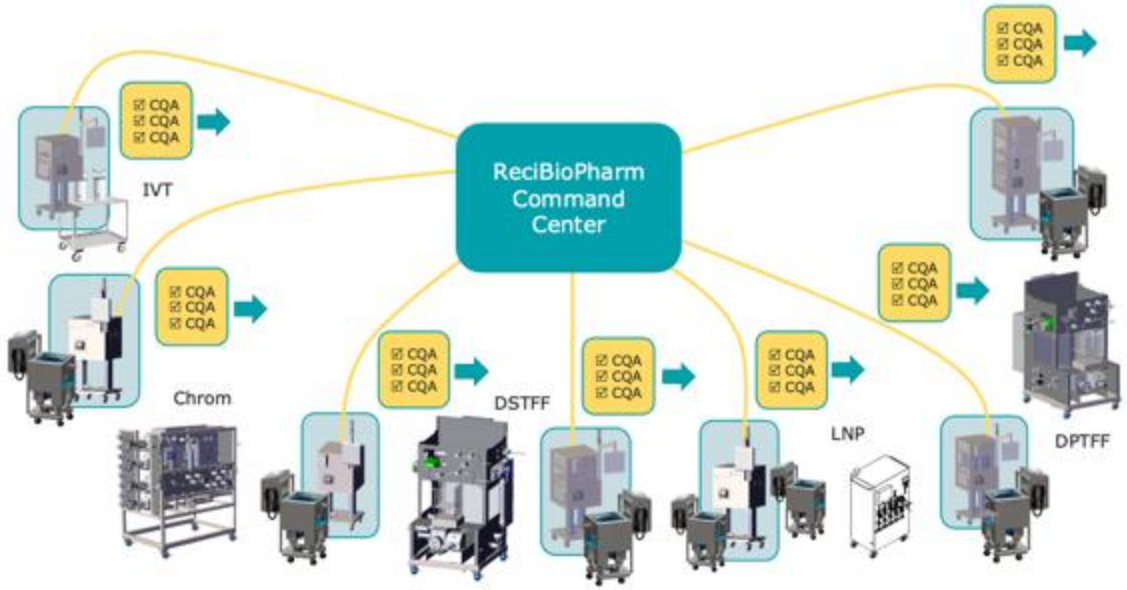
IVT | TFF 1 & 2 | ODT Chrom | Mixing | TFF 3

Individual unit operation with the same PAT toolbox as CP1/2 system

CP1 – PD scale (produces 0.5g/day xRNA)
CP2 – GMP scale (produces 0.5-40g/day xRNA)
CPC – lab scale (factor of 10 smaller then CP1 used for characterization)
*All setups equipped with PAT (E2E)

CP1





CP2 (cGMP)

KNOWLEDGE BIOHUB

(Intelligence Hub)

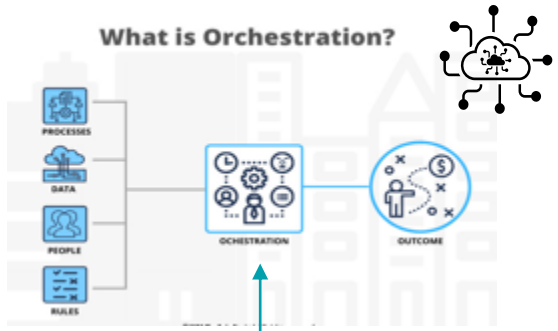
Structured, semi-structured, unstructured data

Data Lake

Knowledge Hub

PD Simulator (Digital DOE calculator)

Streaming analytics/PAT Management Software and data orchestration & diagnostics for preventive maintenance



Digital Twin/Machine Learning

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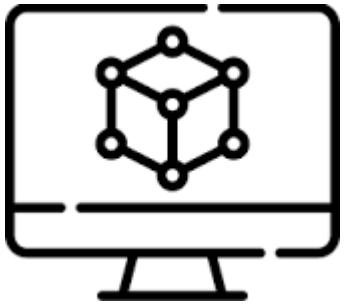
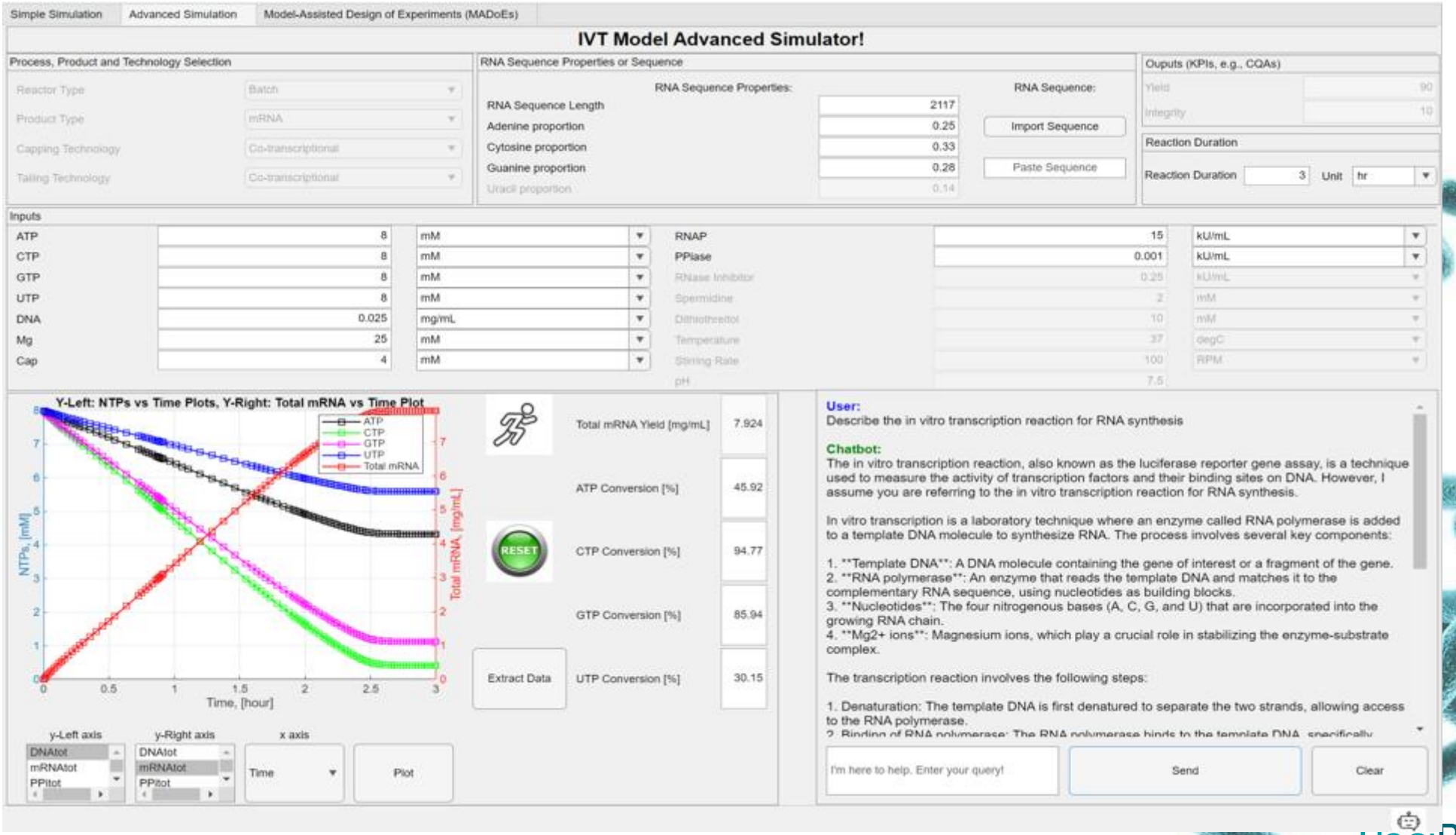
IVT MECHANISTIC MODEL AND SIMULATOR GUI WITH CHATBOT (ADVANCED WINDOW)



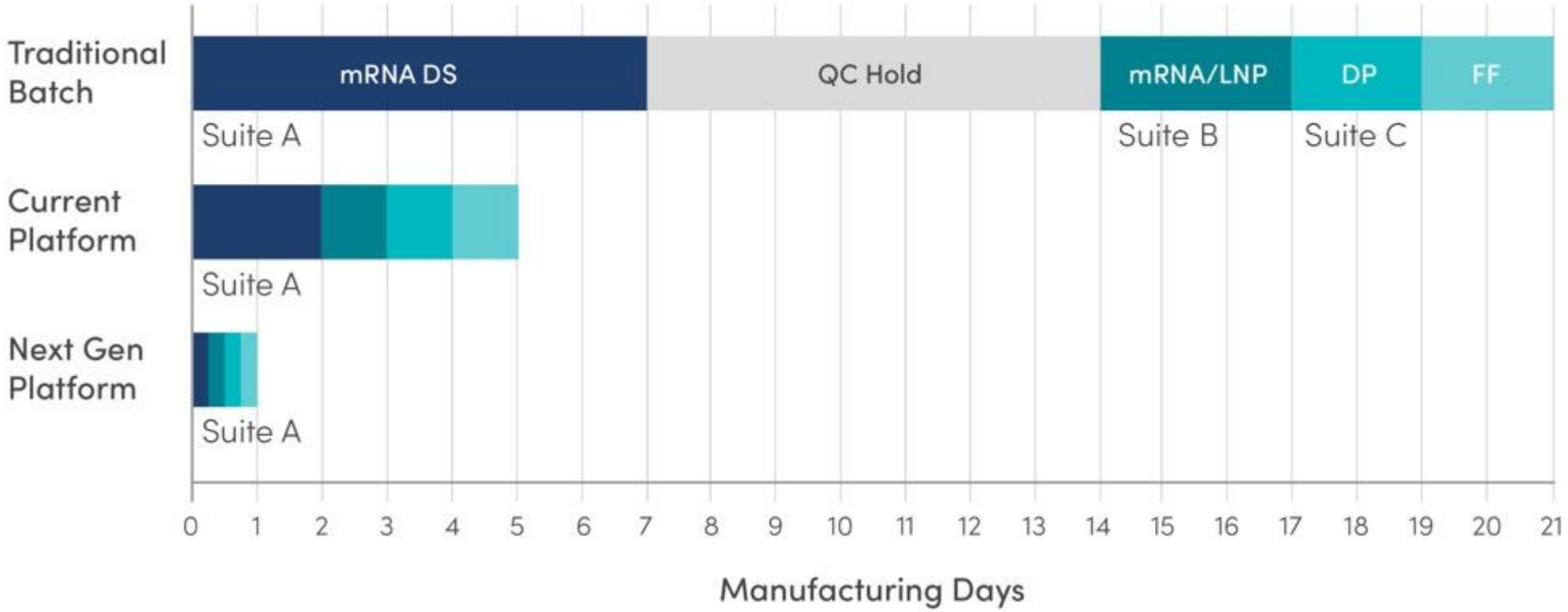
Installable locally

Click to demo on-line!



RESULTS/OUTCOMES

OUTCOME NO. 01: PAT-ENABLED CONTINUOUS PROCESSING ACCELERATES CGMP MANUFACTURING FROM 3 WEEKS TO A SINGLE DAY



- Single-Suite, Single-day process from IVT to fill-finish
- Real time analytics substantially reduces analytics resources and QC hold times

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IN-PROCESS PAT (ASSAY COVERAGE) / ~60% OF CQA'S FOR xRNA HAVE A PAT SOLUTION WITH OTHERS STILL BEING EXPLORED

In-line PAT assay coverage

Step	mRNA concentration - A260 (Nanodrop)	mRNA concentration - Florescence (RiboGreen)	Encapsulation - Florescence (RiboGreen)	mRNA purity - CE (Frag A)	mRNA integrity - CE (Frag A)	mRNA intactness	percentage of fragment mRNA	aggregate quantitation	dsRNA content - Dot blot	LNP size, polydispersity - DLS	LNP surface charge, morphology, ζ-potential	Residual Total Protein - Florescence (NanoOrange)	Residual plasmid DNA - qPCR	Visual Appearance - USP⟨790⟩	Subvisible particles	Particulate matter	Sucrose concentration - LC/CAD	Total lipid (ionizable, PEG, DSPC, cholesterol)	Osmolality - mOsm/kg H_2O	Viscosity - USP⟨911⟩	Residual ethanol - GC	Residual solvents	Residual *E.coli* HCP - ELISA	Residual nucleotides, NTP - LC/MS	pH	Bioburden, Sterility - USP⟨1⟩, ⟨61⟩, ⟨71⟩	Endotoxin - USP⟨85⟩	5' Capping Efficiency - LC/MS	3' Poly(A) tail length, variant distribution - LC/MS	Sequence identification - Illumina, Sanger	IVT potency - cell-based assay	mRNA purity - LC, CE, Bioanalyzer?	mRNA content - UPLC and Rib green	mRNA/Lipid Mass (N:P ratio)	Extractable Volume	Container Closure integrity (CCIT)
IVT Reaction	x																																			
IVT Pool	x				x				x			x	x										x	x			x	x	x	x	x					
IVT Pool Dilution	x																																			
TFF1 Pool	x				x				x			x	x										x	x			x	x								
TFF1 Dilution	x																																			
Oligo dT Pool	x			x	x				x			x	x										x	x			x	x								
TFF2 Pool/Release DS	x			x	x	x		x	x			x	x	x								x	x	x	x		x	x	x	x	x	x	x			
Lipid Solution																		x																		
DS Dilution	x			x																					x											
LNP Pool		x	x							x																	x							x		
TFF3 Pool		x	x							x																x	x									
Post-Sucrose		x	x							x							x		x							x	x									
Bulk DP		x	x		x					x				x			x								x	x	x									
Release DP		x	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x

Assay coverage for mRNA process

Steps of the mRNA process aligned to assays per unit operation

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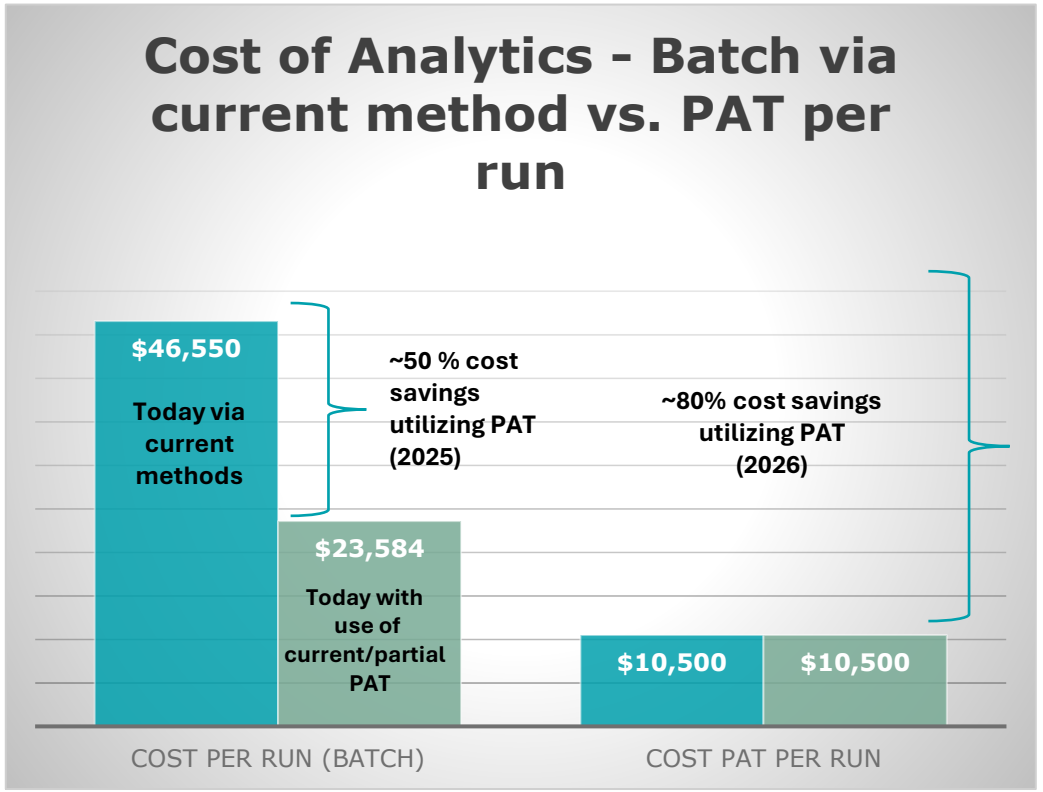
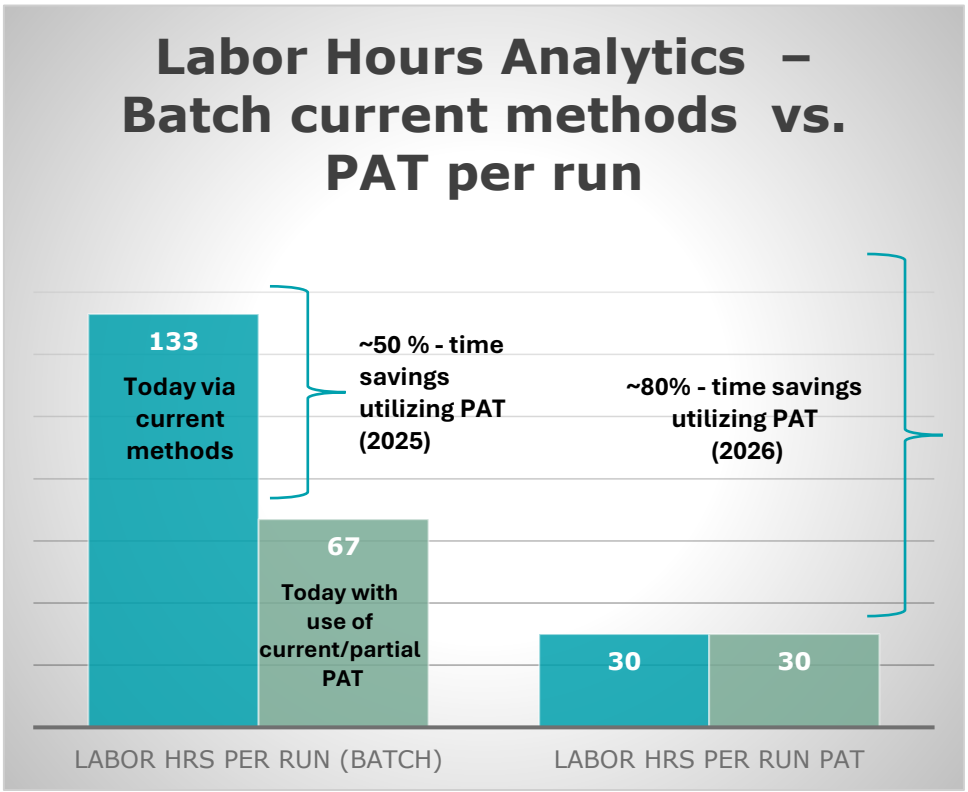
OUTCOME NO. 02: QC TESTING | SAVES TIME, MONEY AND REDUCES OUT OF SPECIFICATION OCCURRENCES





- Today we are at ~50% cost and time savings on analytical testing per run
- In 2026 we plan to be at ~80 % cost and time savings by bringing in more in-line PAT tools into process

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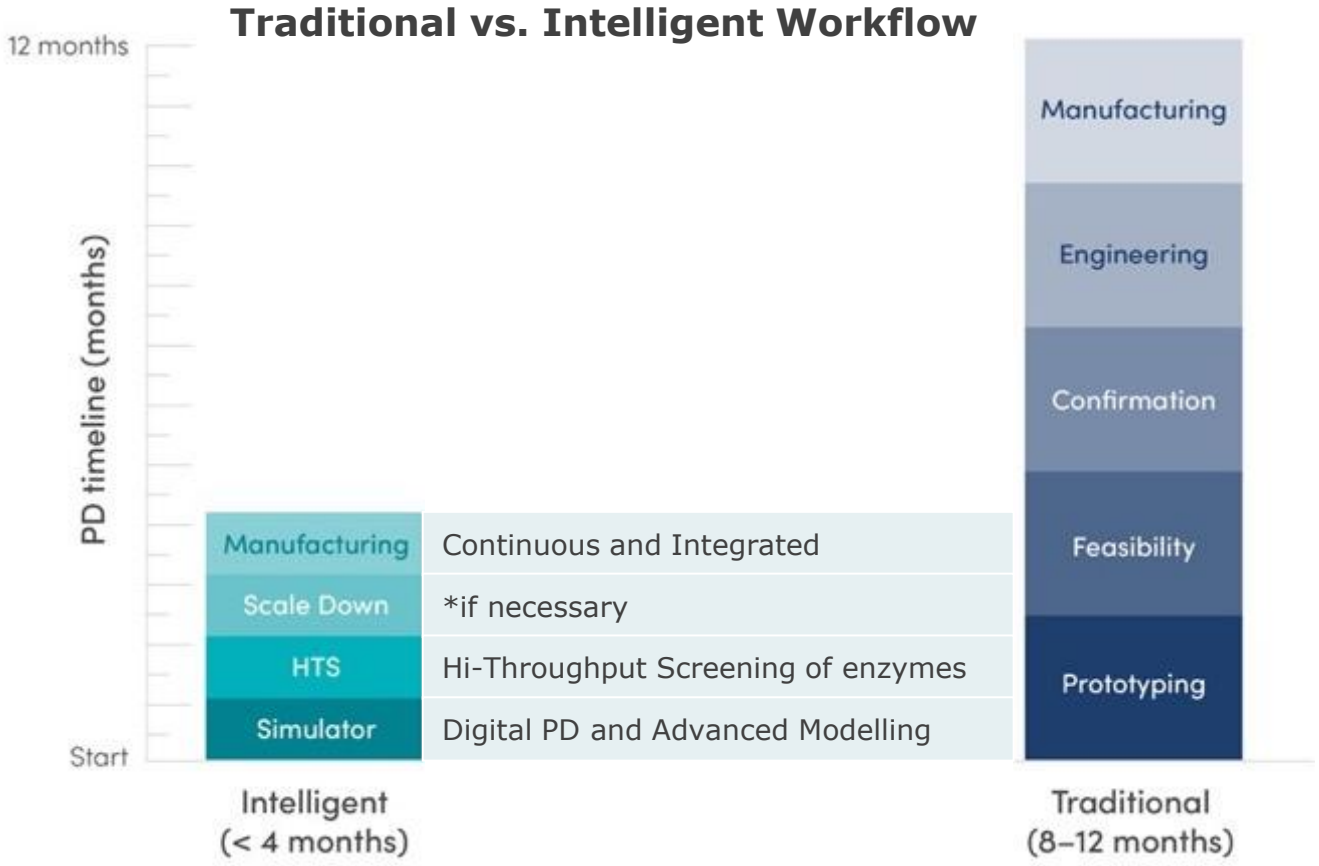
OUTCOME NO. 03: PAT OFFERS A MORE INTELLIGENT APPROACH TO PD | A HOLISTIC APPROACH TO TECHNOLOGY AND PROCESS DEVELOPMENT

A PARADIGM SHIFT IN HOW PROGRAMS WILL DEVELOP



FUTURE INNOVATIONS HELPING GMP CUSTOMERS TODAY

Knowledge and tools spun out of FDA grant program

- ❑ T7 Polymerase platform
- ❑ Cell-free DNA platform
- ❑ Cap Analogs

Continued tech dev planned including:

- ❑ High throughput screening
- ❑ Knowledge Hub
- ❑ More accurate QC tests

QUALITY | INTEGRATED CP PROCESS DEMONSTRATES EQUIVALENT PERFORMANCE FOR DS AND DP MANUFACTURING COMPARING TO BATCH MODEL

mRNA construct	Process model	mRNA					mRNA/LNP			
		Purity, A260/A280	mRNA integrity	dsRNA residue	Enzyme residue	DNA residue	mRNA integrity	EE%	Particle size	PDI
Construct #1 (2400nt)	Batch model	1.82	91%	<1%	<1 ug/mL	0.17 ng/mg	91%	93%	64 nm	0.02
	Continuous model	1.91	93%	<1%	1.96 ug/mL	0.37 ng/mg	91%	94%	60 nm	0.05
Construct #2 (4500nt)	Batch model	1.74	89%	<1%	1.8 ug/mL	0.05 ng/mg	87%	90%	62 nm	0.03
	Continuous model	1.77	88%	<1%	1.2 ug/mL	0.22 ng/mg	n/a	88%	60 nm	0.04

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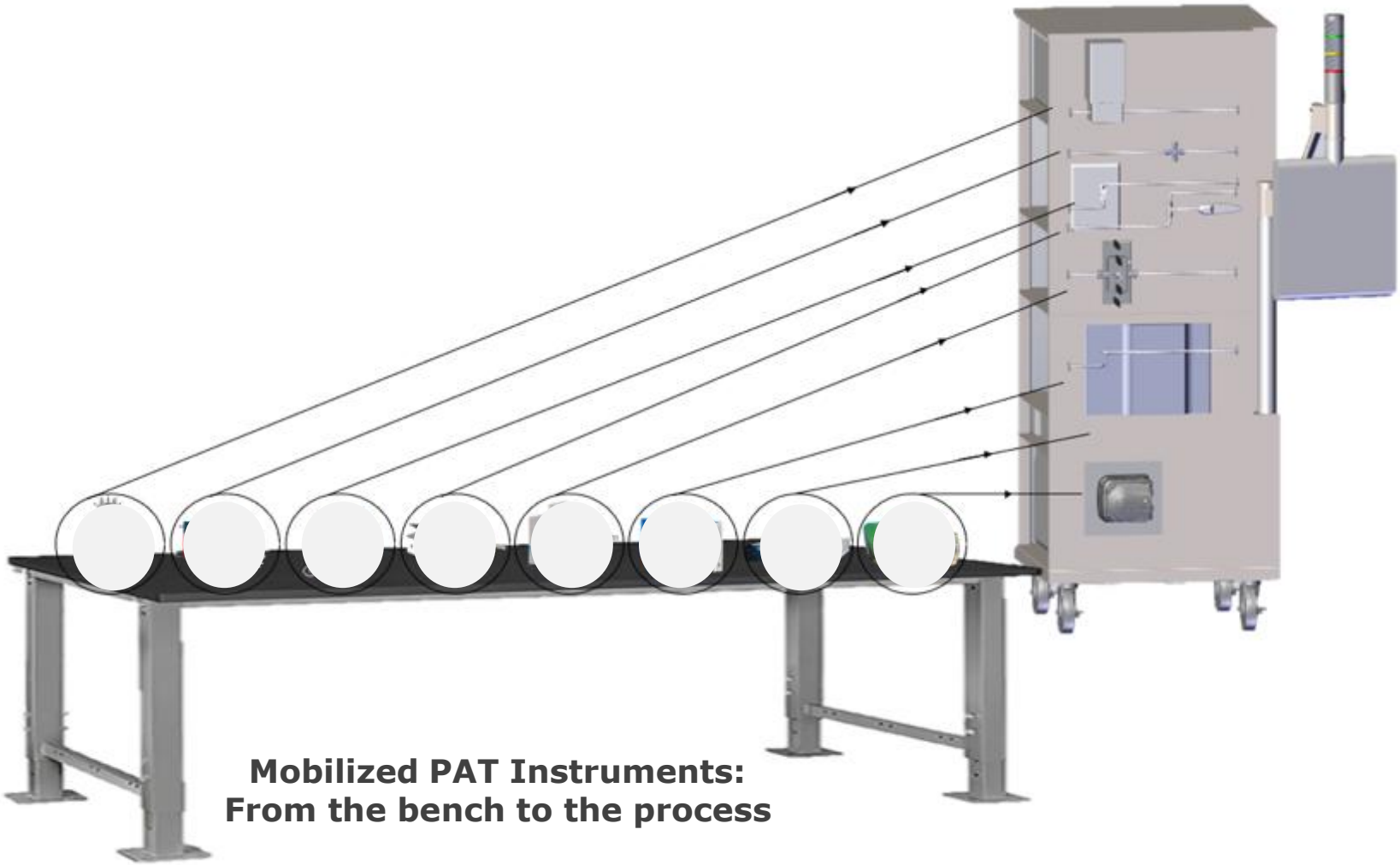
ENABLING TECHNOLOGIES AND VALUE TO THE INDUSTRY

INTRODUCING PAT-SKID | THE CORE ENABLING TECHNOLOGY "QC ON WHEELS" THAT IS THE LINCHPIN SOLUTION



Mobilized PAT Instruments:
From the bench to the process

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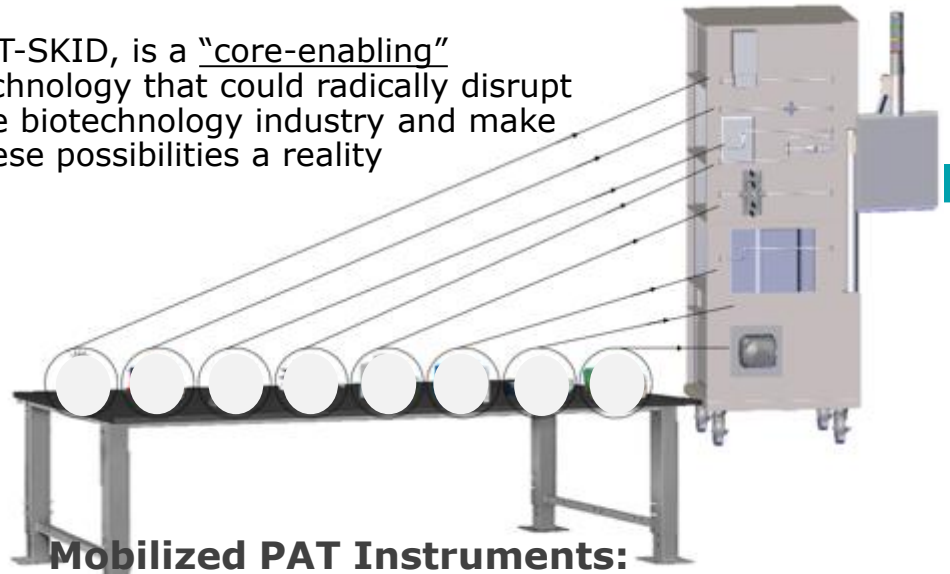
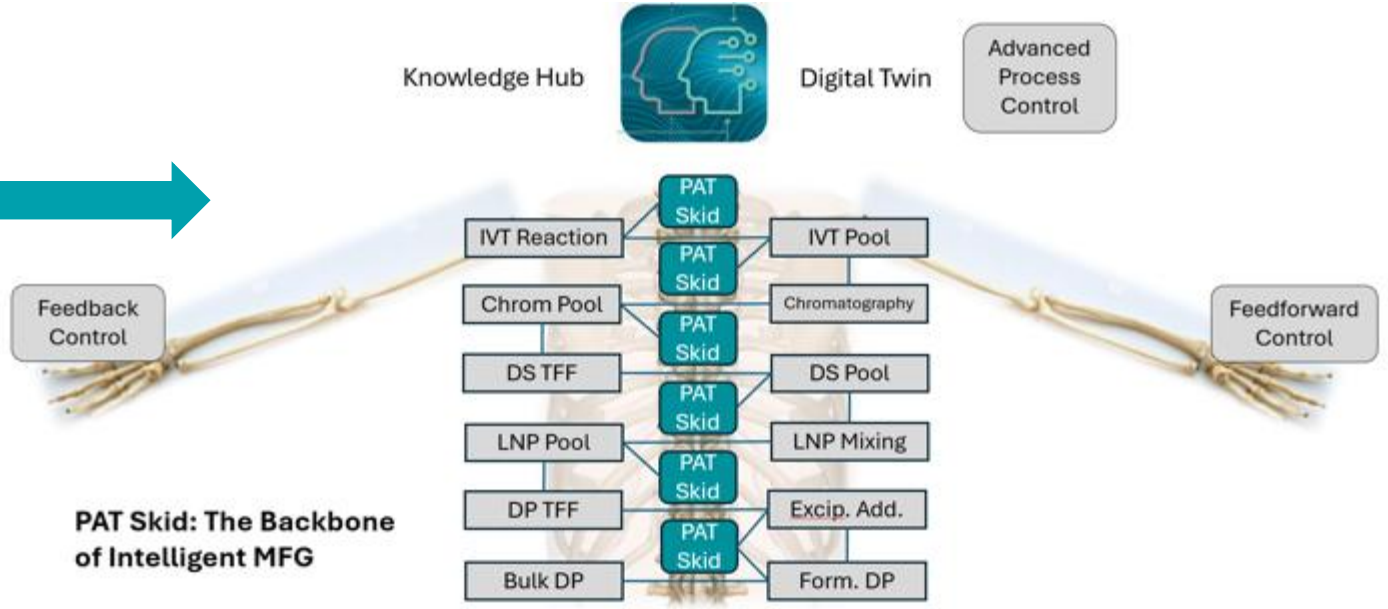
HAD TO DEVELOP A NEW TECHNOLOGY TO MAKE HAPPEN (PAT-RNA) | PAT SKID: THE BACKBONE OF INTELLIGENT MFG

- PAT-SKID, is a "core-enabling" technology that could radically disrupt the biotechnology industry and make these possibilities a reality



Mobilized PAT Instruments: From the bench to the process



- Engineered to house most PAT instruments
- Connections are process skid agnostic
- Allows manufacturing processes to be fully integrated
- Can be used with most modalities (liquid required)
- Digital architecture will be modality & process unit agnostic
- Allows for a single "Smart Control Center"

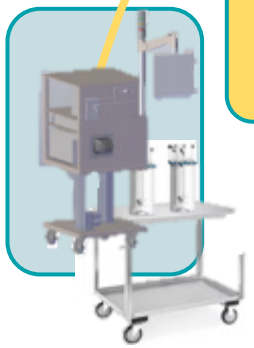
CP2/PAT SKID DATA FLOW: REAL TIME MONITORING AND RELEASE

PAT SKID: (THE "MICRO-CHIP")

ReciBioPharm Command Center

☑ CQA
☑ CQA
☑ CQA

IVT



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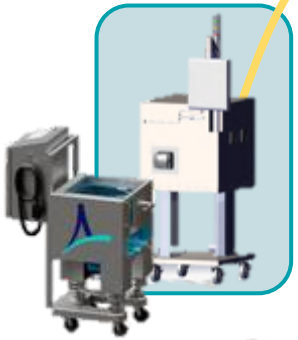
Chrom



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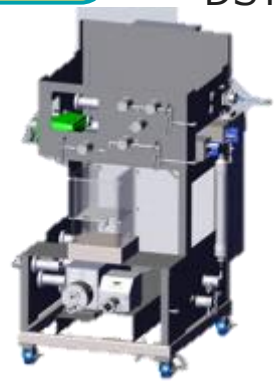
DSTFF



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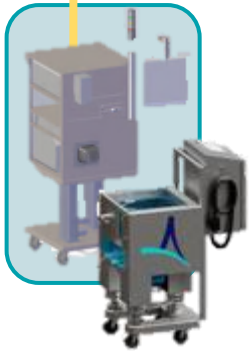

☑ CQA
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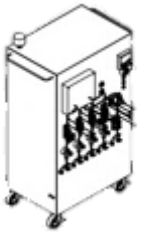
LNP



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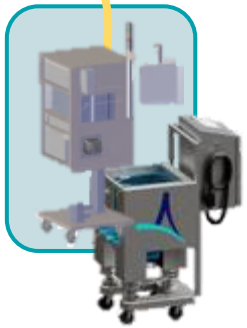

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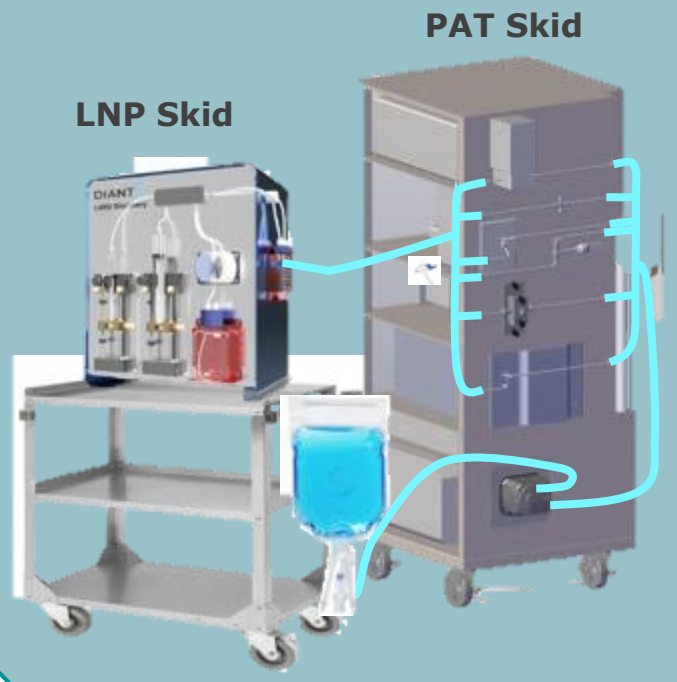
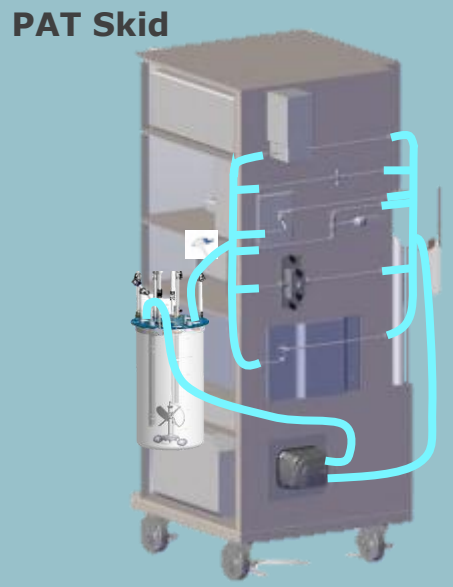
WHY IS IT A GAME CHANGER? | UTILITY, MOBILITY, ADAPTABILITY AND SPEED TO COLLECT/PROCESS ANALYTICAL DATA

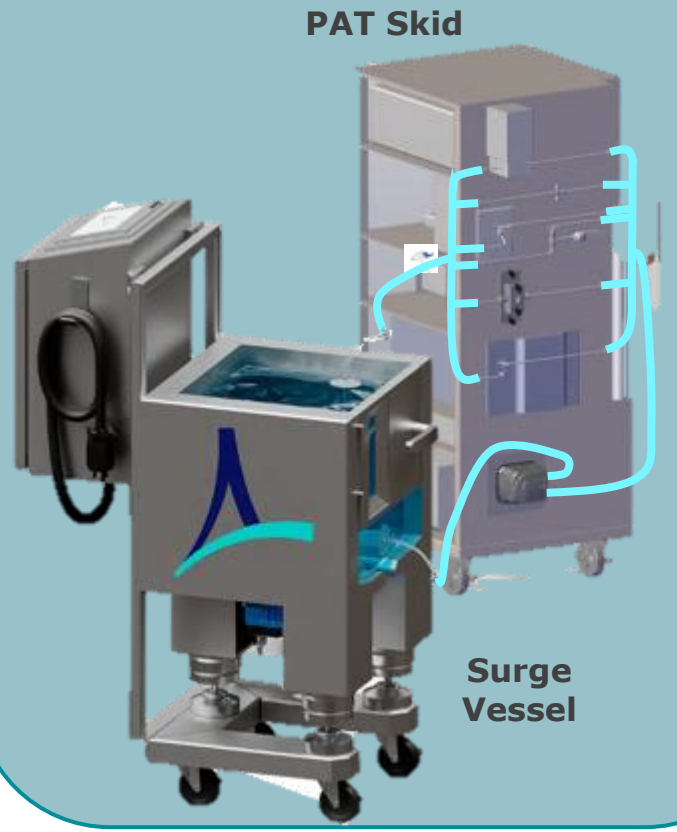
Process/Analytical Development



QC Labs

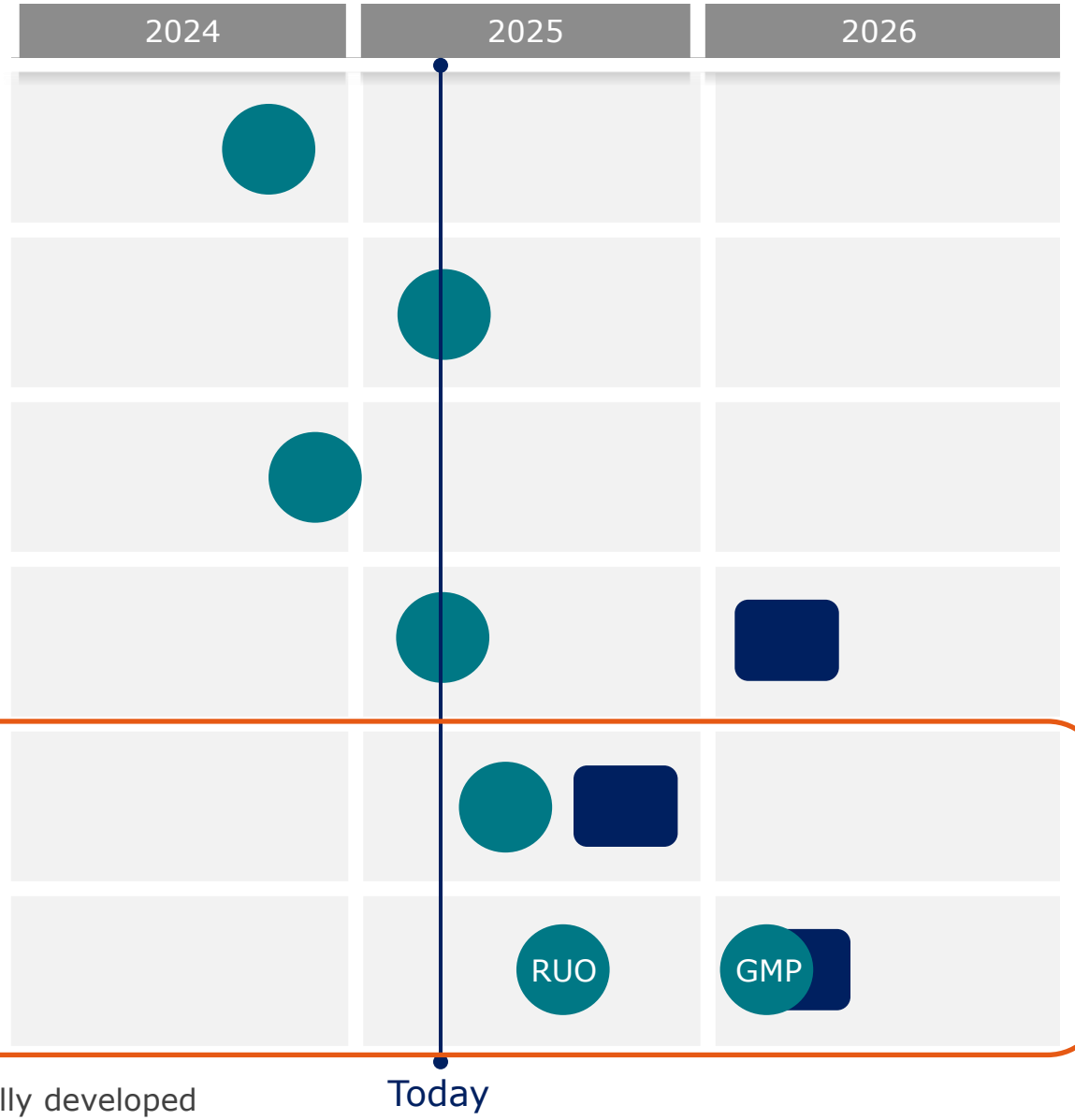


Manufacturing



TECHNOLOGY ROADMAP

Capability	Definition	Purpose
HTS	Micro-scale screening platform to optimize reagents	Fast screening of T7, LNP, and capping technology
CPC	Scale down system for data generation and PD verification	Lower cost data development
CP1*	Small-scale RUO technology proving ground	Process Development and optimization studies
Simulator	Digital PD program leveraging knowledge hub and ML	Fast, low-cost Process Development
Standalone PAT-Skid	A single bioprocessing skid that centralizes PAT	QC on Wheels; Real Time Release Testing, Data for Model Generation
CP2	Small-Large cGMP manufacturing train with Digital Twn and PAT	Rapid clinical quality RNA



*to be phased out once platform is fully developed

CONCLUSIONS

- ATMPs are in desperate need of platforms for development and manufacturing
- We are poised to radically disrupt how biologics are being developed and manufactured today, by providing a bundle of hardware, consumables, software and services to achieve intelligence-driven development (iD) and manufacturing (iM)
- Our iD/iM platforms will reduce process development and manufacturing timelines by at least 50% and will only improve over time
- The enabling technology developed, PAT-SKID, makes that possible (think intel chip)
- The industry and regulators are excited about our approach (PAT-SKID)
- The possibilities of PAT-SKID for H_2O, Buffers, other modalities is tremendous

ACKNOWLEDGEMENT

Team would like to thank our development partner, MIT, and FDA for grant funding this development

Thank you for your attention!