



Finding What Matters

Implementing Review-by-Exception RtReports
for Manufacturing at BioMarin

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BIOMARIN[®]

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Finding What Matters isn't always easy...

The image is a collage representing the complexity of finding information in a data-rich environment. It features multiple overlapping windows from the BIOMARIN software interface. The windows display various data elements:

- BIOMARIN®** logos and the tagline "Matching proven science with proven needs".
- Recipe information: "Recipe: PR_ Ba", "Batch ID: C", "PART_3".
- Report details: "RtReport: Chromatography", "Rev. 1.0", "Effective Date: 1", "Page 13 of 17".
- Alarm logs: "01-Apr-19 09:58:16 PM ALARM", "01-Apr-19 11:10:15 PM ALARM", "01-Apr-19 11:18:22 PM OPERATOR".
- Timestamp lists: Multiple columns of timestamps starting from "01-Apr-19 01:53:04 PM" and ending at "01-Apr-19 03:48:08 PM".
- Page numbers: "Page 15 of 17", "Page 17 of 17".

In the center of the collage is a circular inset image. It shows a person in a grey suit standing in front of a bookshelf, holding a large, thick stack of papers that completely obscures their face. Above the person's head, a sign reads "HELP!". This visual metaphor suggests the overwhelming volume of data and the difficulty of identifying the most important information.

About BioMarin

First-in-class or best-in-class
therapeutics for patients with
rare genetic diseases

MOLECULE/INDICATION
ALDURAZYME® (laronidase) FOR MPS I
NAGLAZYME® (galsulfase) FOR MAROTEAUX-LAMY / MPS VI
KUVAN® (sapropterin dihydrochloride) FOR PKU (GLOBAL, EXCEPT JAPAN)
FIRDAPSE® (amifampridine phosphate) FOR LEMS (EU)
VIMIZIM® (elosulfase alfa) FOR MORQUIO A SYNDROME / MPS IVA
BRINEURA® (cerliponase alfa) FOR CLN2 DISEASE
PALYNZIQ® (pegvaliase-pqz) FOR PKU
VOSORITIDE (BMN 111) ANALOG OF CNP FOR ACHONDROPLASIA
VALOCTOCOGENE ROXAPARVOVEC (BMN 270) AAV-FACTOR VIII FOR HEMOPHILIA A
VOSORITIDE (BMN 111)* ANALOG OF CNP FOR DOMINANT INHERITED SHORT STATURE
BMN 307 AAV GENE THERAPY FOR PKU
BMN 331 AAV GENE THERAPY FOR HEREDITARY ANGIOEDEMA (HAE)

*Study is being developed in a collaboration

Manufacturing Operations



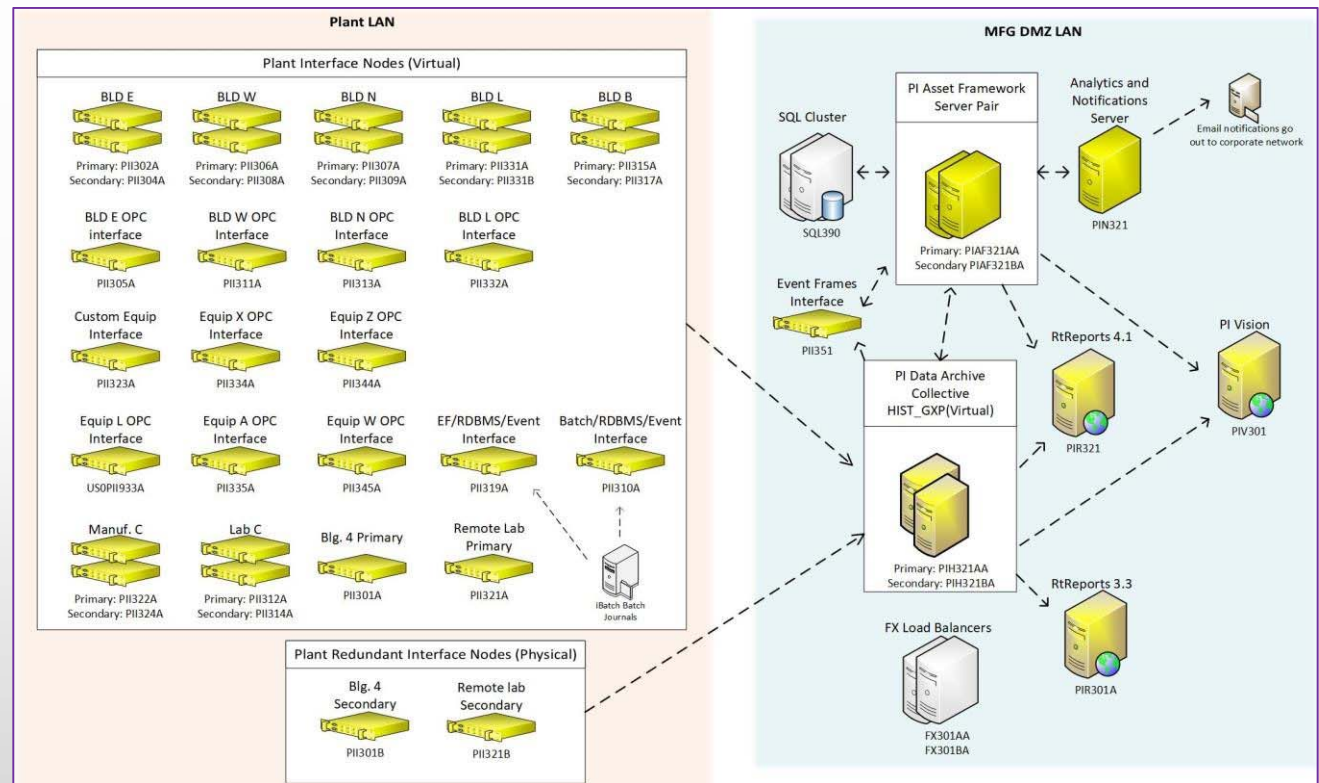
Novato, California



Shanbally, Ireland

PI at BioMarin

- Enterprise Agreement with OSIsoft
- Regional PI Systems for each site
- GMP, Non-Validated, and Test Environments

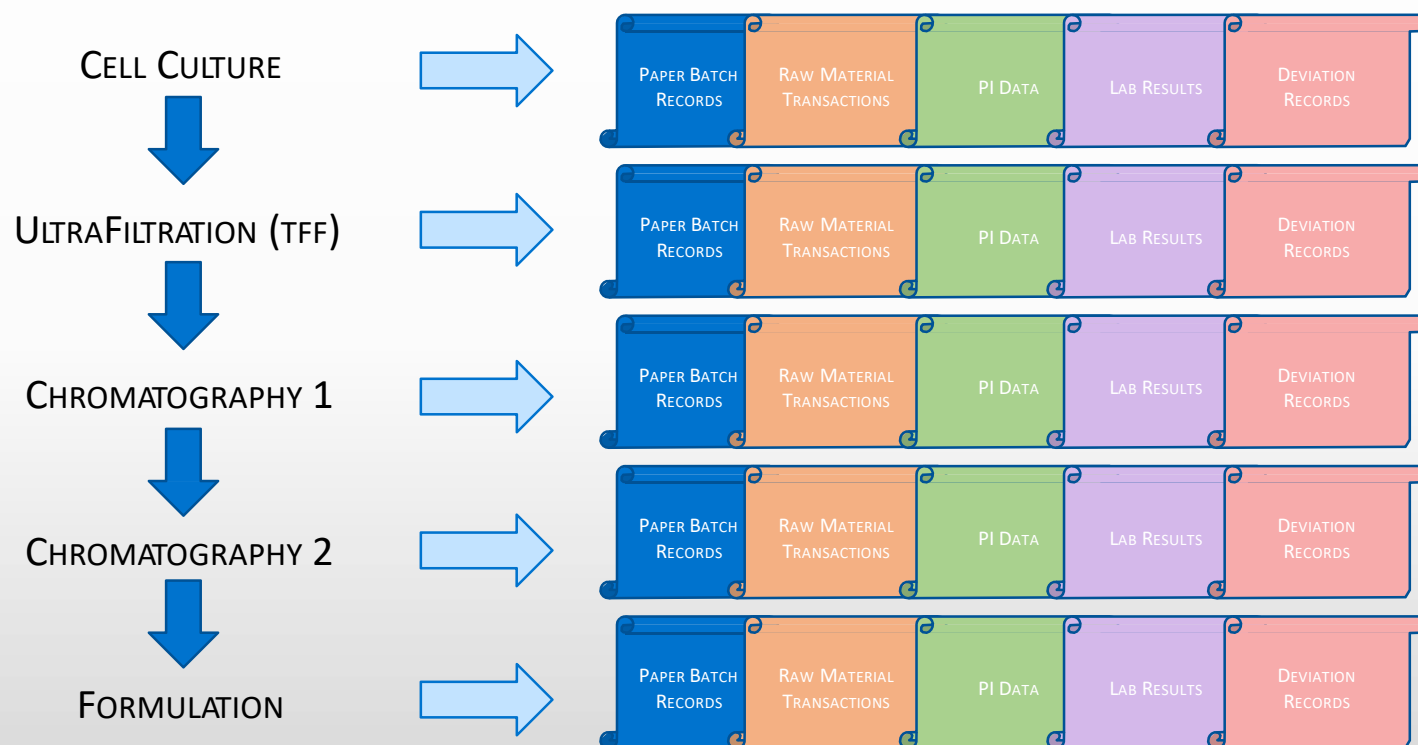


Novato GMP PI System

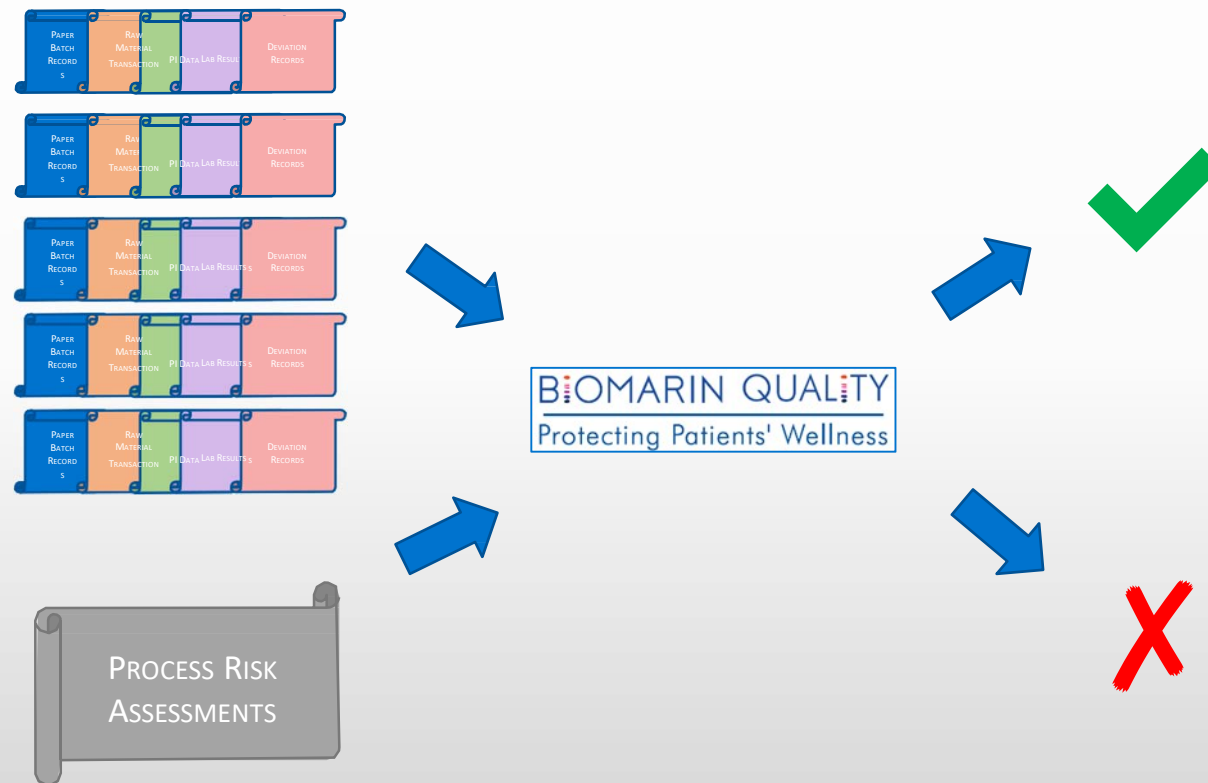
Finding What Matters

Review-by-Exception Reporting:
Legacy Lot Release Process

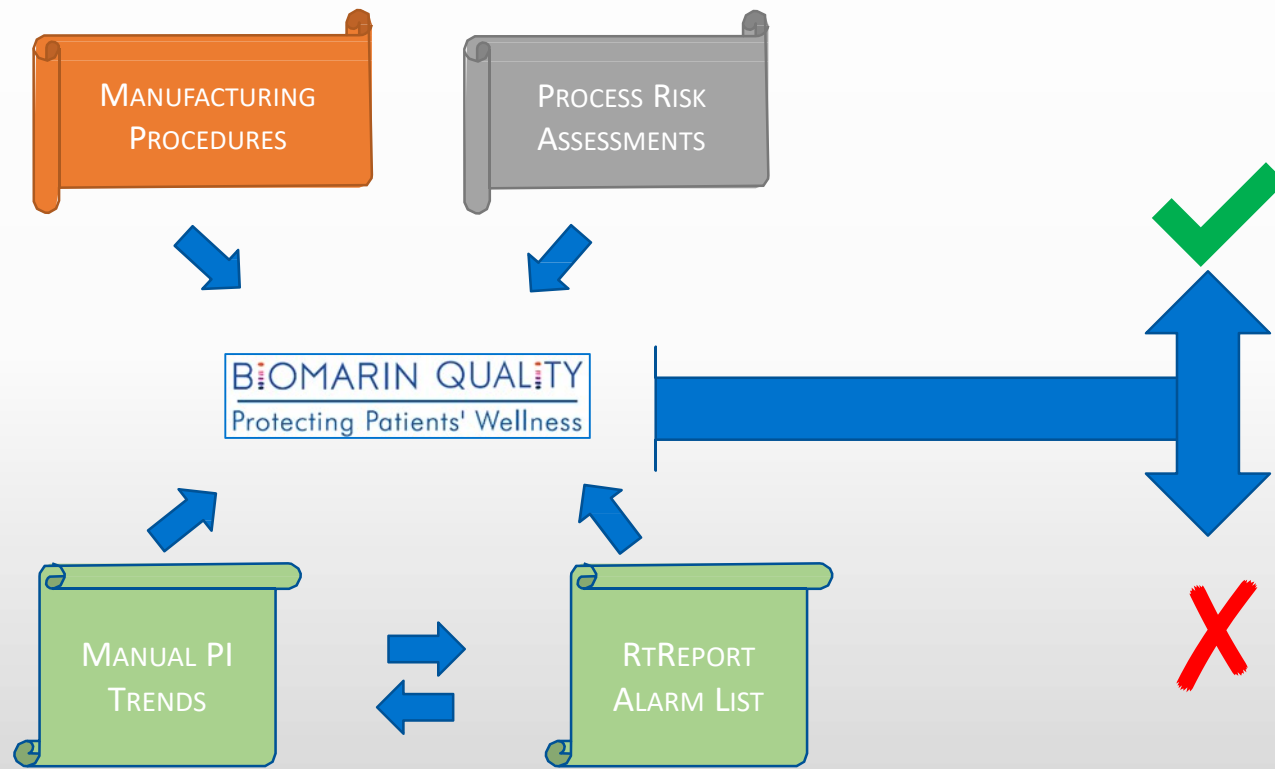
Legacy Lot Release Process



Legacy Lot Release Process

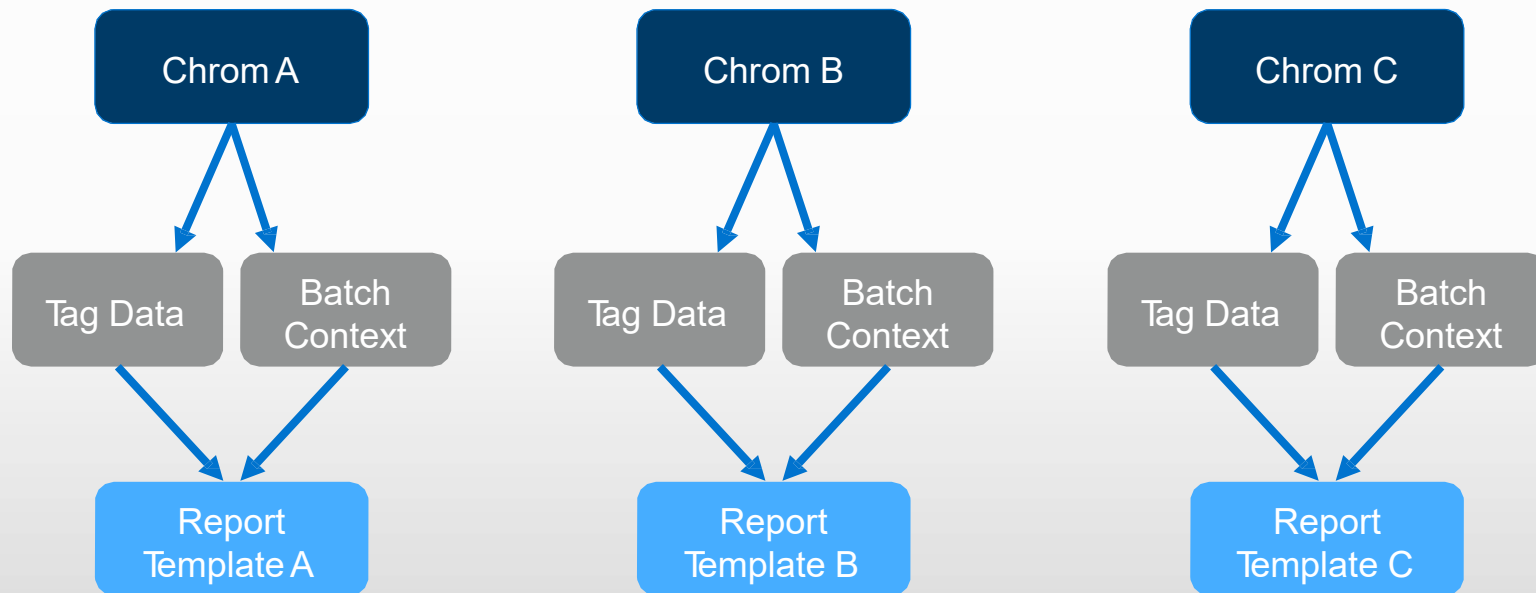


Legacy Lot Release Process



Legacy Lot Release Process

Report development for individual equipment rather than groups of systems



Legacy Lot Release Process - Problem Statement

ISSUE	EFFECT
Reports include unnecessary information	↑ QA review time
Reports lack necessary information	QA manually reviews trends
Reports are not templated	Solution is not scalable

Finding What Matters

Review-by-Exception Reporting:
Path Forward

Finding What Matters

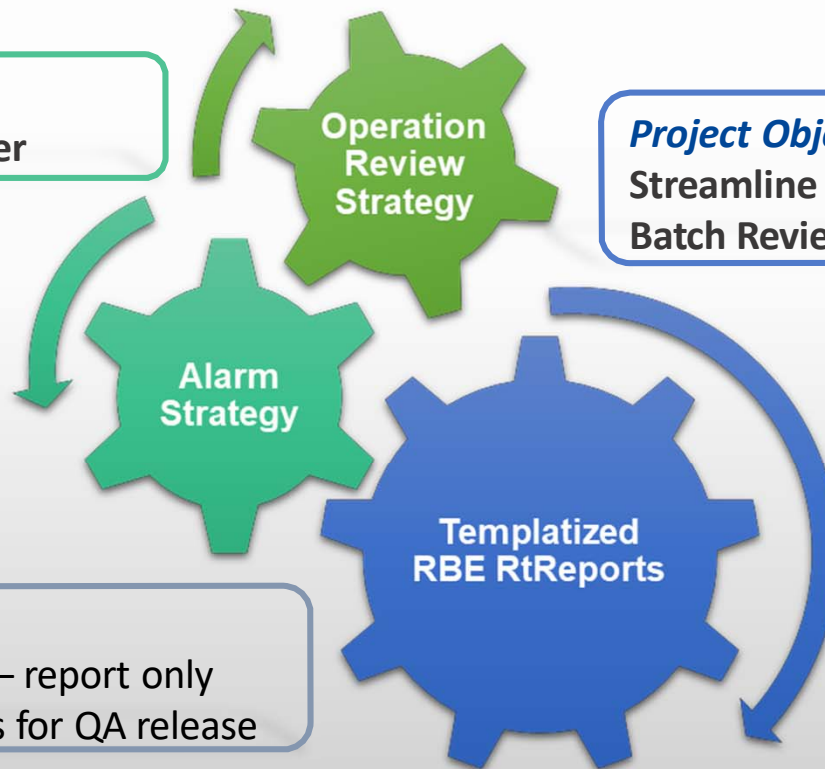
Implementing Review-by-Exception RtReports
for Manufacturing at BioMarin

Site Goal:

Get Products to Patients Faster

Project Objective:

Streamline and Standardize QA
Batch Review



Project Output:

Review-by-Exception – report only
contains what matters for QA release

Path Forward: Operation Review Strategy



- Focus on what matters
 - Not all parameters are equal
 - Report on what is key to efficacy and critical to patient safety
- Assign a QA Review Strategy to each Critical Parameter
 - Batch Record Review, Review-By-Exception, RtReport Trend etc.

Parameter	Quality Critical?	Measured Online?	Measurement is robust?	Alarmable?	RBE?
<i>Flush Volume</i>	X				X

Path Forward: Operation Review Strategy



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Parameter	Quality Critical?	Measured Online?	Measurement is robust?	Alarmable?	RBE?
Flush Volume	X				X
Step Yield	✓	X			X

Path Forward: Operation Review Strategy



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Parameter	Quality Critical?	Measured Online?	Measurement is robust?	Alarmable?	RBE?
Flush Volume	X				X
Step Yield	✓	X			X
OD	✓	✓	X		X

Path Forward: Operation Review Strategy



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Parameter	Quality Critical?	Measured Online?	Measurement is robust?	Alarmable?	RBE?
Flush Volume	X				X
Step Yield	✓	X			X
OD	✓	✓	X		X
UV	✓	✓	✓	X	X

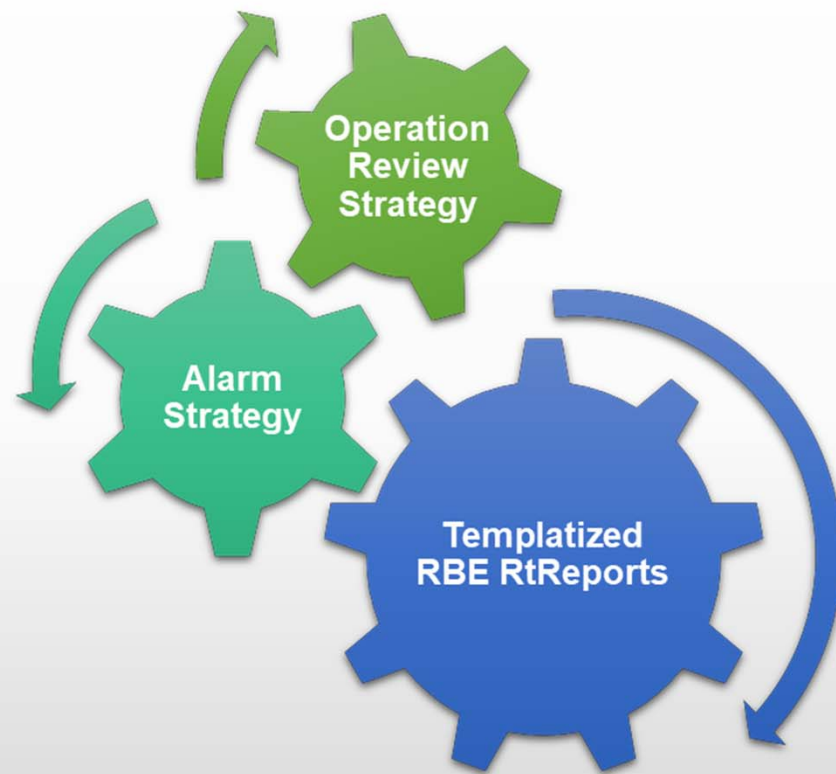
Path Forward: Operation Review Strategy



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 - Report on what is key to efficacy and critical to patient safety
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Parameter	Quality Critical?	Measured Online?	Measurement is robust?	Alarmable?	RBE?
Flush Volume	X				X
Step Yield	✓	X			X
OD	✓	✓	X		X
UV	✓	✓	✓	X	X
pH	✓	✓	✓	✓	✓

Reviewed by other means



Path Forward: Alarm Strategy



GOAL: Alarm configuration where alarms serve as **binary classifiers**

➤Exception vs. No Exception

PREREQUISITES:

1. HIHI and LOLO Alarms are only enabled **during critical steps**
2. HIHI and LOLO Alarms are only enabled for **critical parameters**
3. Alarms trigger at Acceptable Limits
➤Defined by Process Risk Assessment

Path Forward: Alarm Strategy

CASE 1:

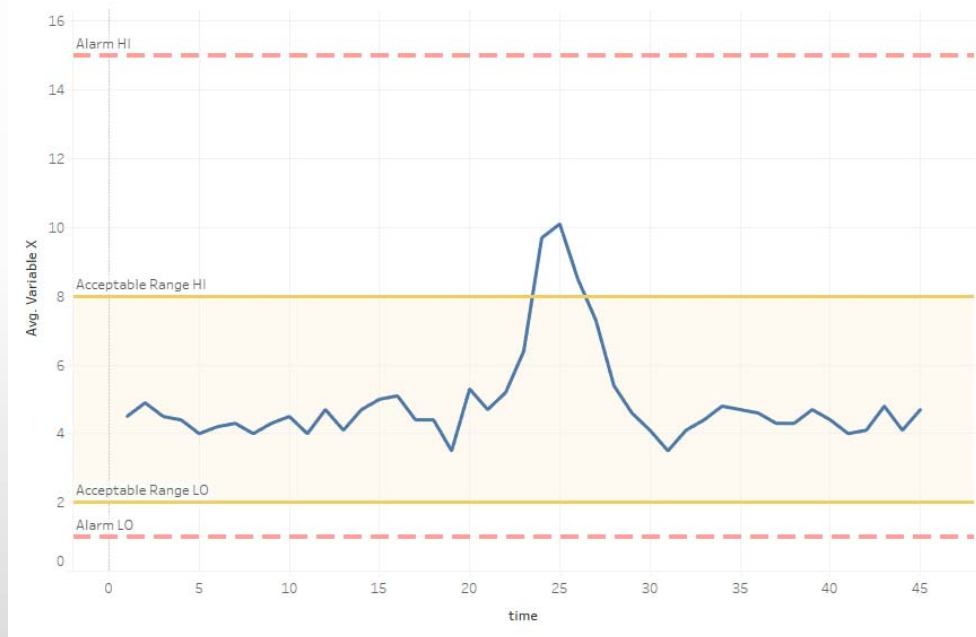
- Excursion but no Alarm
- False Negative

IMPACT:

- QA Manual Review of PI Data

SOLUTION:

- Set Alarm Limits = Acceptable Range



Simulated process data shown

Path Forward: Alarm Strategy



CASE 2:

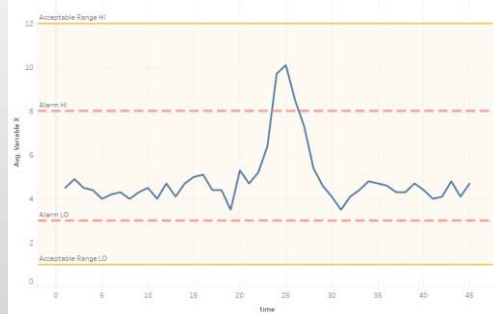
- Alarm but no Excursion
- False Positive

IMPACT:

- Nuisance Alarms
- Unnecessarily long RtReport

SOLUTION:

- Set Alarm Limits = Acceptable Range



CASE 3:

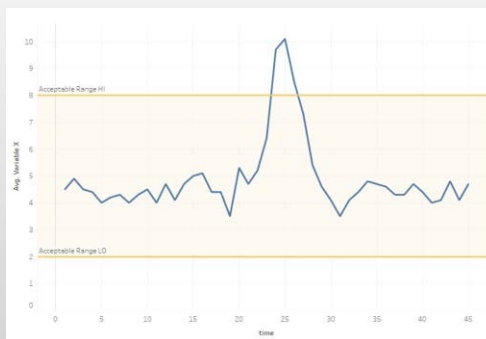
- No Alarms Defined

IMPACT:

- QA Manual Review of PI Data

SOLUTION:

- Set Alarm Limits = Acceptable Range



CASE 4:

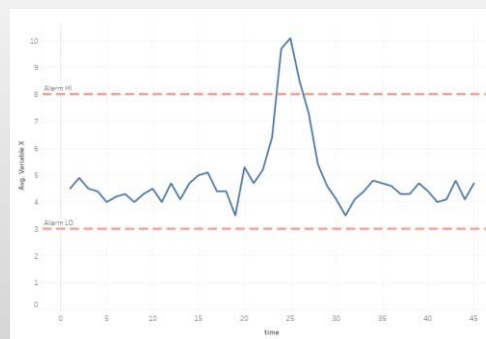
- Alarmed but no Range Defined

IMPACT:

- Unnecessarily long RtReport

SOLUTION:

- Remove Alarms, non-impactful process parameter



Path Forward: Alarm Strategy

CASE 5:

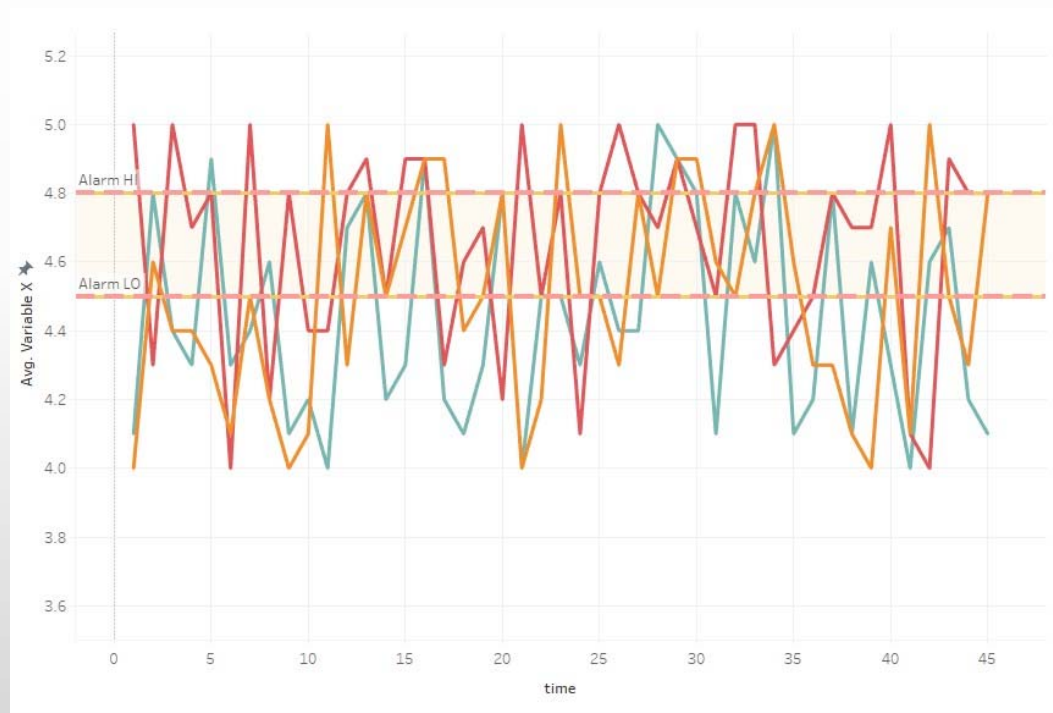
- Acceptable Range is not representative of process/measurement capability

IMPACT:

Nuisance alarms for non-critical parameters

SOLUTION:

- Use process history (*PI Web API*) and SME input to recommend appropriate range/alarms



Path Forward: Alarm Strategy

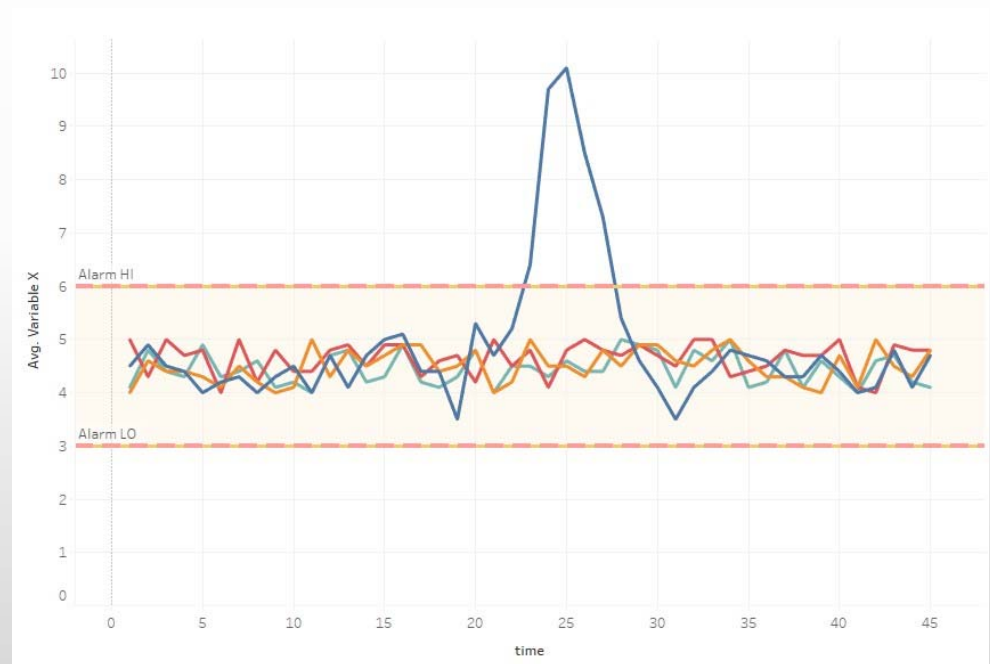


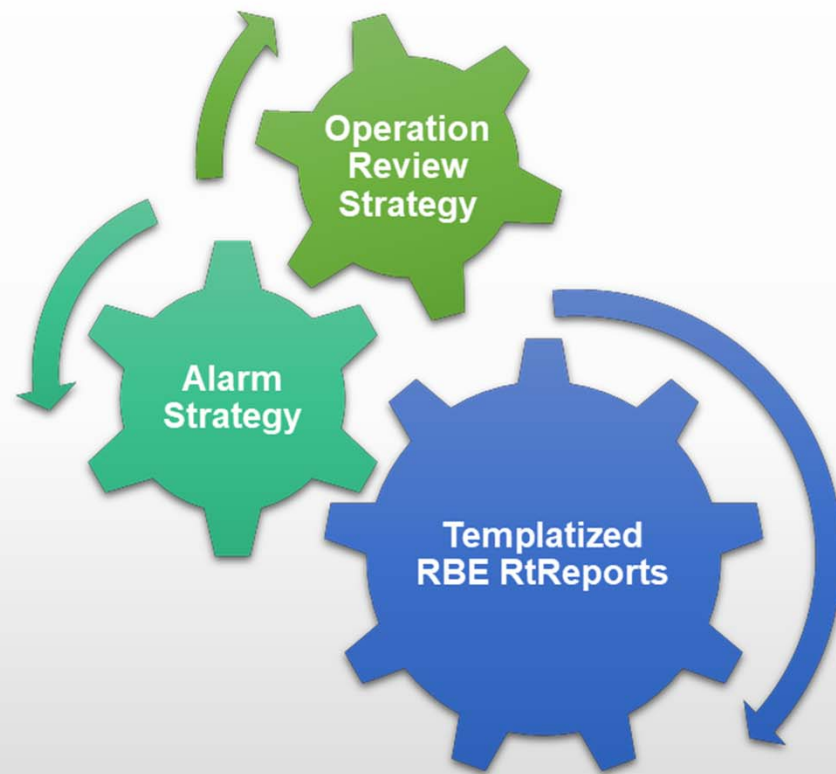
Final State:

- Alarms match acceptable ranges, serve as classifiers of true process excursions

Result:

- RBE report only shows instances of excursions which require review





Path Forward: Templatization



Project enabled by Key PI System Upgrades

PI Asset Framework 2018

- Event Frames
- Templates

PI RtReports 4.1

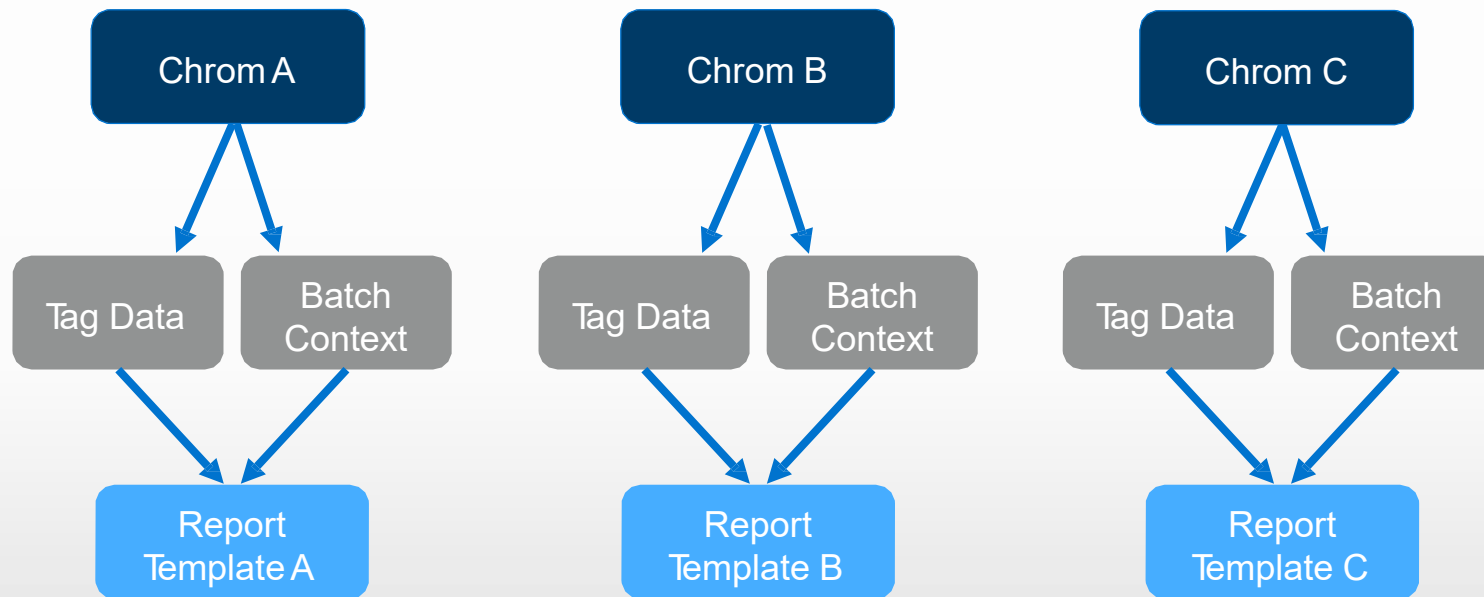
- Build validated report templates using EFs

PI Vision & PI Web API

- Real time monitoring of EFs
- Efficient queries of historical data

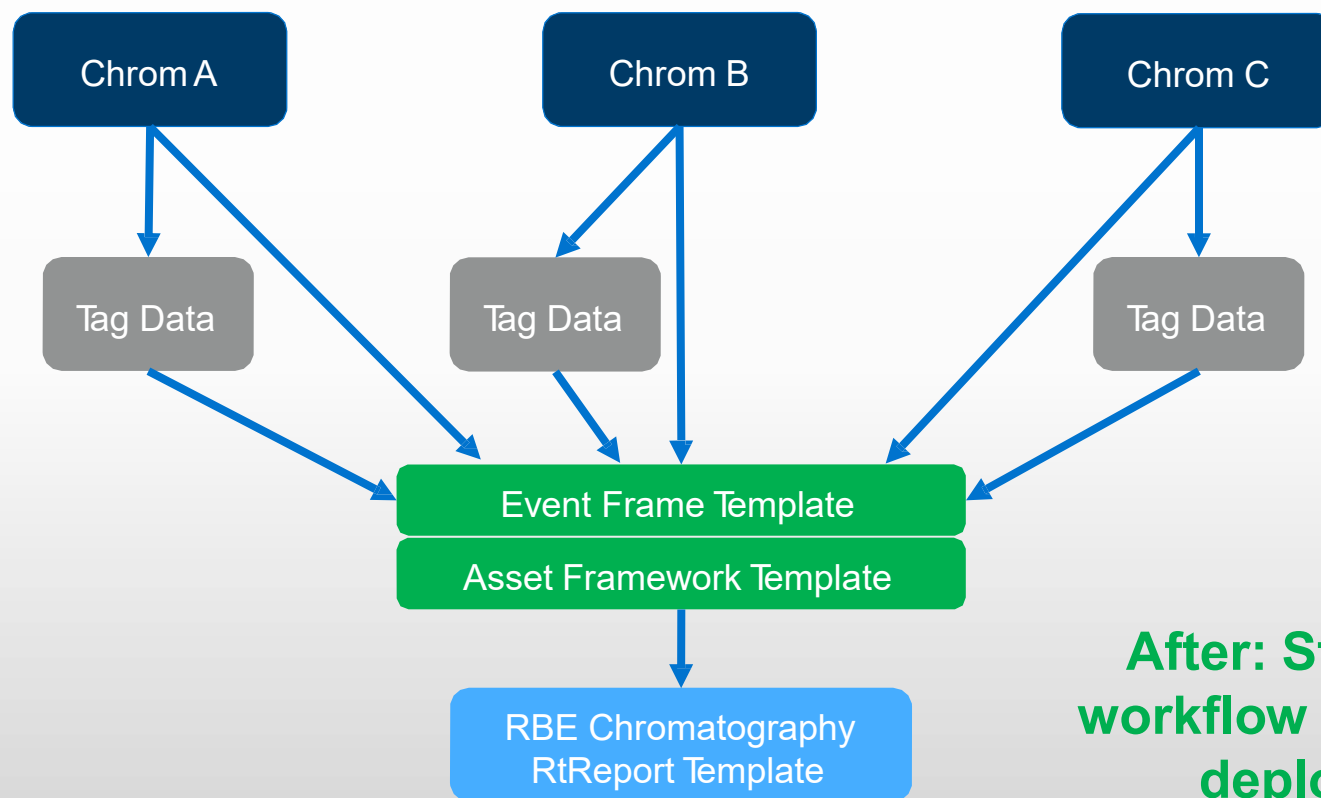
Templatized approach using Event Frames

Path Forward: Templatzation



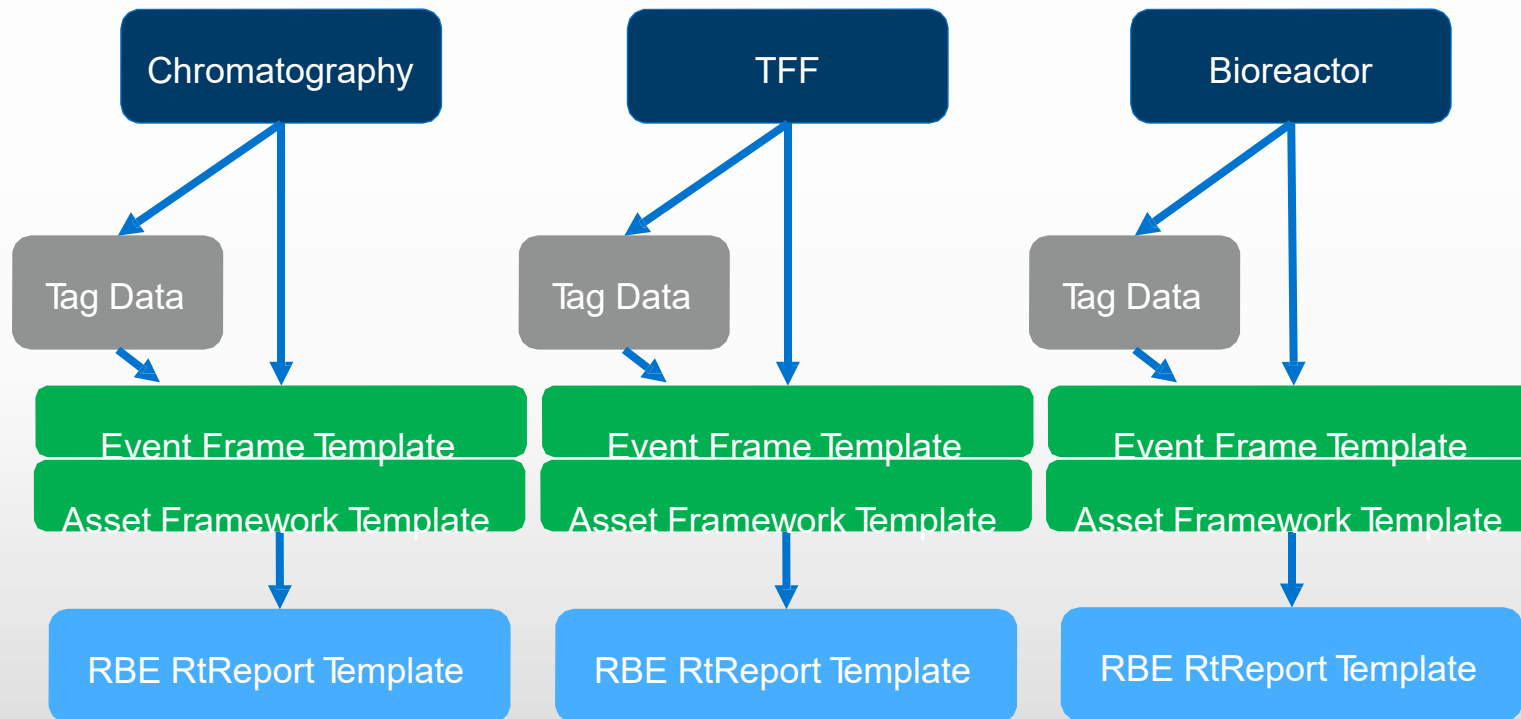
Before: Not a scalable approach...

Path Forward: Before and After



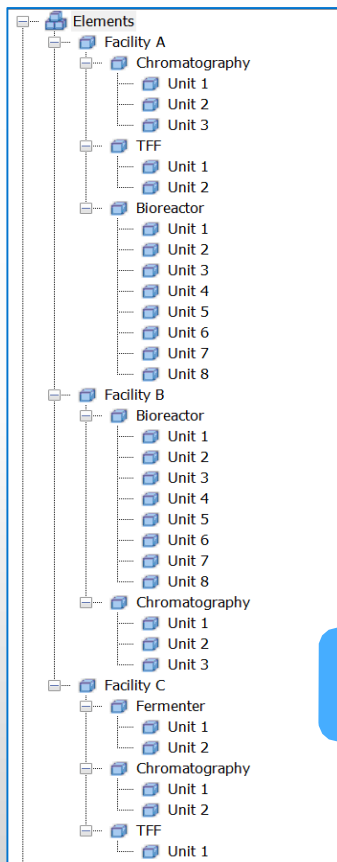
After: Streamlined workflow for RtReport deployment!

Path Forward: Templatization



Templates can cover all units of an equipment type

Path Forward: Templatization



Chromatography Review-By-Exception	TFF Review-By-Exception	Bioreactor Review-By-Exception
General Attribute Templates Ports Analysis Templates Notification	General Attribute Templates Ports Analysis Templates Notification	General Attribute Templates Ports Analysis Templates Notification
Filter	Filter	Filter
Category: Equipment Info Category: Exception Parameter 1 Pre Trap Conductivity Pre Trap Conductivity HIHI Alarm Pre Trap Conductivity HIHI Enabled Pre Trap Conductivity HIHI Limit Pre Trap Conductivity LOLO Alarm Pre Trap Conductivity LOLO Enabled Pre Trap Conductivity LOLO Limit Category: Exception Parameter 2 Category: Exception Parameter 3 Category: Exception Parameter 4 Category: Substitution Parameters Category: Trended Parameters	Category: Equipment Info Category: Exception Parameter 1 Category: Exception Parameter 2 Permeate Flow Rate LOLO Limit Permeate Flow Rate LOLO Enabled Permeate Flow Rate LOLO Alarm Permeate Flow Rate HIHI Limit Permeate Flow Rate HIHI Enabled Permeate Flow Rate HIHI Alarm Permeate Flow Rate Category: Exception Parameter 3 Category: Exception Parameter 4 Category: Exception Parameter 5 Category: Exception Parameter 6 Category: Substitution Parameters Category: Trended Parameters	Category: Equipment Info Category: Exception Parameter 1 Category: Exception Parameter 2 Category: Exception Parameter 3 Harvest pH Harvest pH HIHI Alarm Harvest pH HIHI Enabled Harvest pH HIHI Limit Harvest pH LOLO Alarm Harvest pH LOLO Enabled Harvest pH LOLO Limit Category: Exception Parameter 4 Category: Exception Parameter 5 Category: Substitution Parameters Category: Trended Parameters



RBE RtReport Template

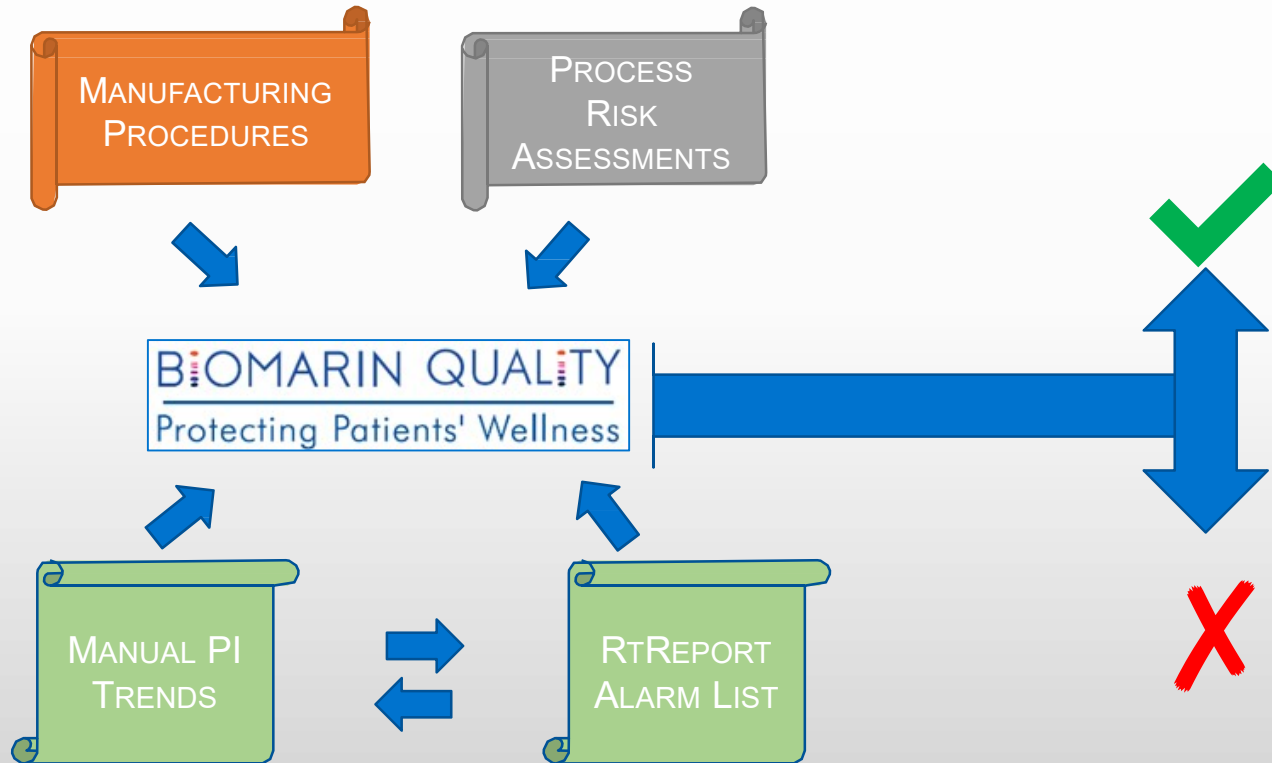
RBE RtReport Template

RBE RtReport Template

3 sets of Template Qualification covers 30 units

Path Forward: Review-by-Exception RtReports

Before: Multiple Checks by QA



Path Forward: Review-by-Exception RtReports



After: Single source to verify batch outcome



Path Forward: Review-by-Exception RtReports

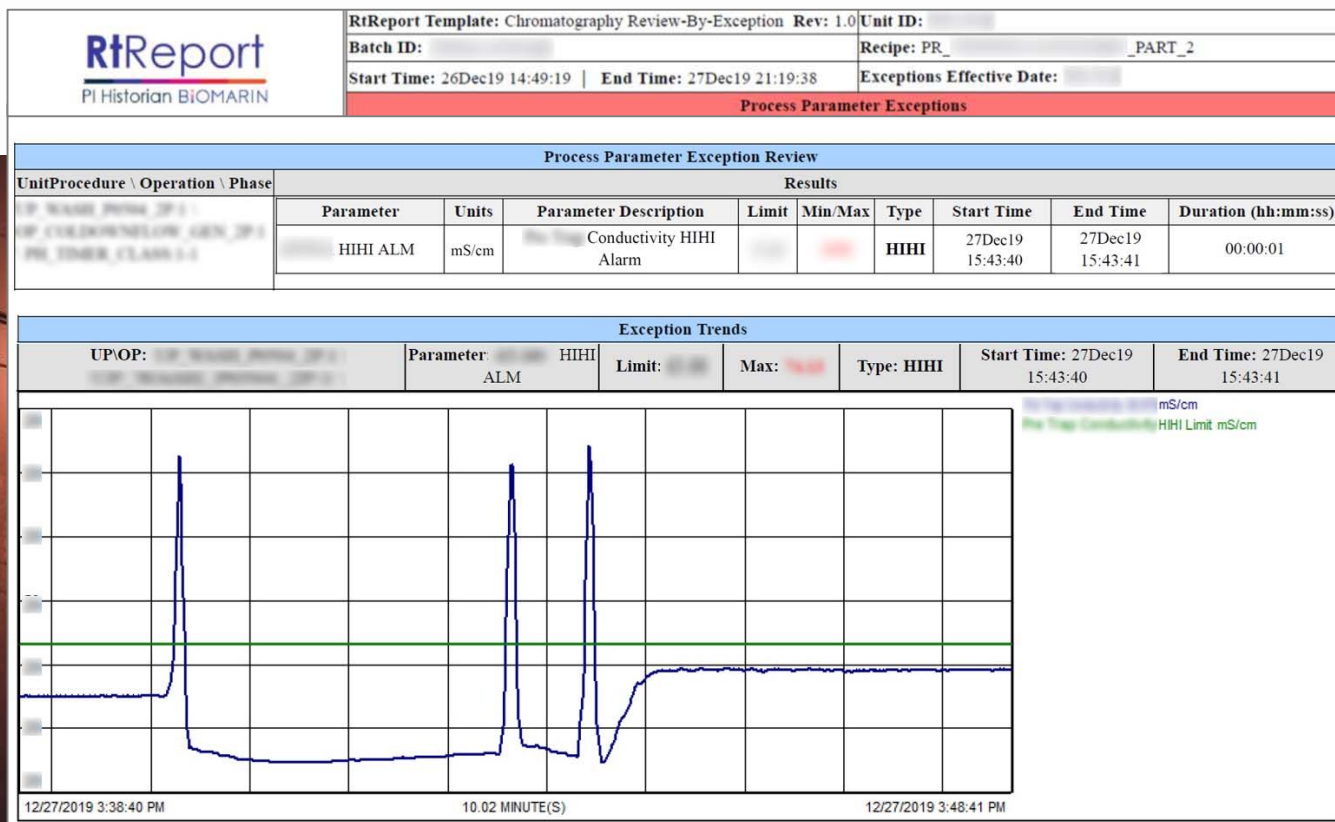
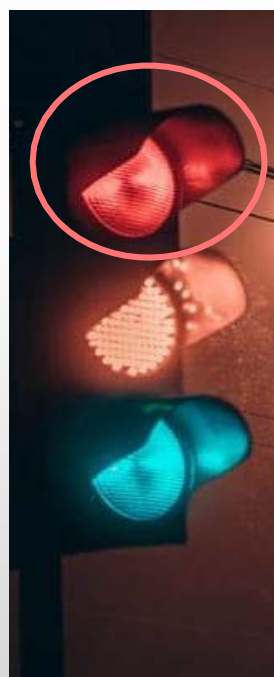
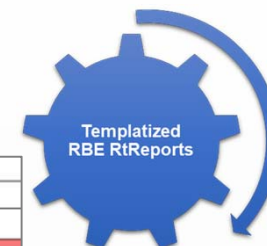


Exception status indicated in RtReport header

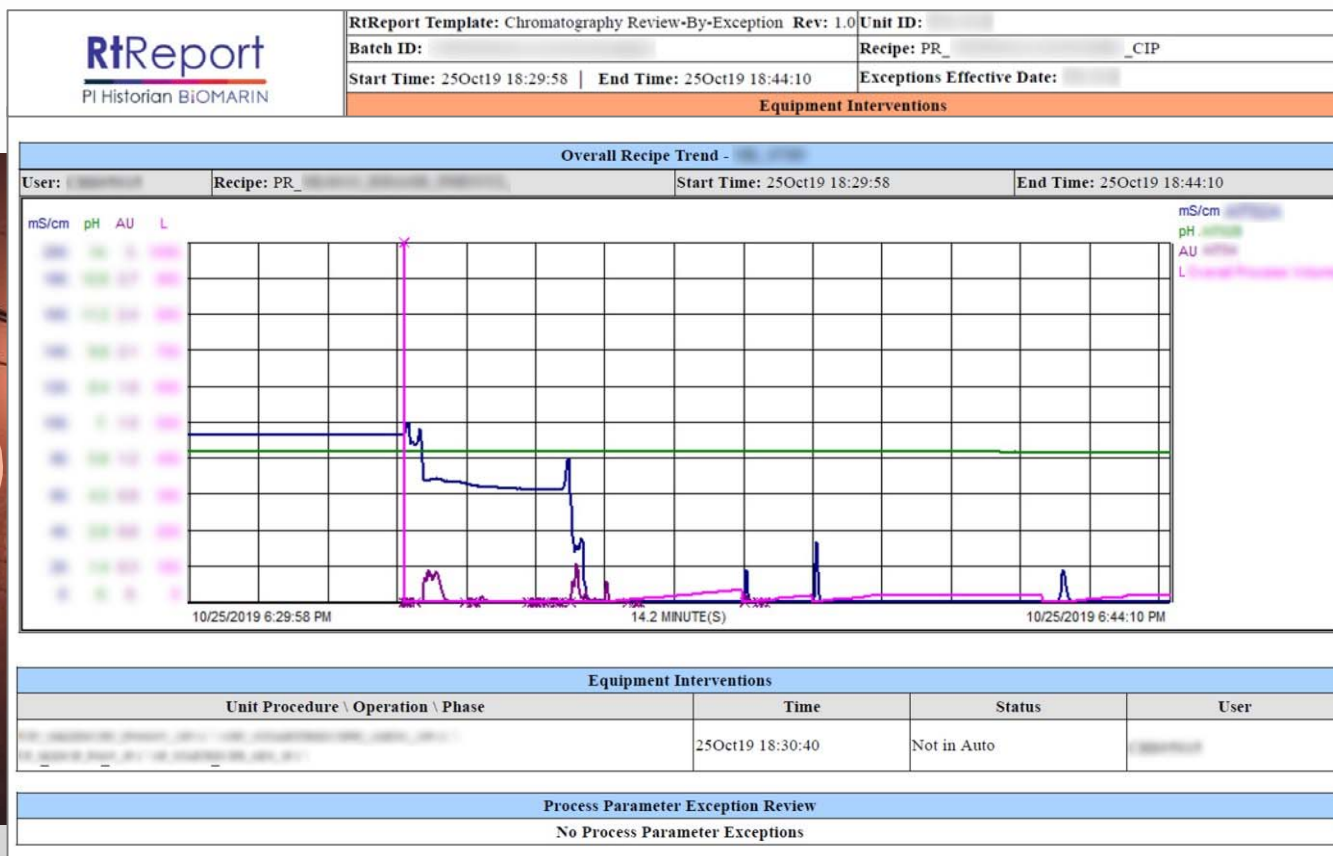
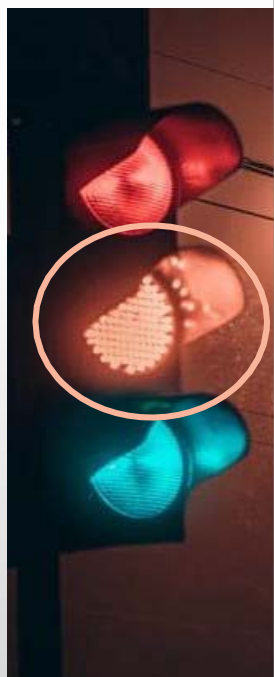
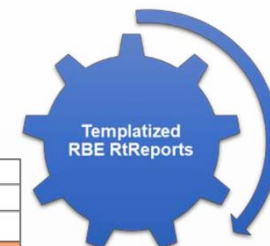


 PI Historian BiOMARIN	RtReport Template: Chromatography Review-By-Exception Rev: 1.0		Unit ID: [REDACTED]
	Batch ID: [REDACTED]	Recipe: PR_ [REDACTED] _PART_2	
	Start Time: 26Dec19 14:49:19	End Time: 27Dec19 21:19:38	Exceptions Effective Date: [REDACTED]
	Process Parameter Exceptions		
 PI Historian BiOMARIN	RtReport Template: Chromatography Review-By-Exception Rev: 1.0		Unit ID: [REDACTED]
	Batch ID: [REDACTED]	Recipe: PR_ [REDACTED] _CIP	
	Start Time: 25Oct19 18:29:58	End Time: 25Oct19 18:44:10	Exceptions Effective Date: [REDACTED]
	Equipment Interventions		
 PI Historian BiOMARIN	RtReport Template: Chromatography Review-By-Exception Rev: 1.0		Unit ID: [REDACTED]
	Batch ID: [REDACTED]	Recipe: PR_ [REDACTED] _PART_2	
	Start Time: 24Dec19 12:40:33	End Time: 24Dec19 18:58:00	Exceptions Effective Date: [REDACTED]
	No Exceptions		

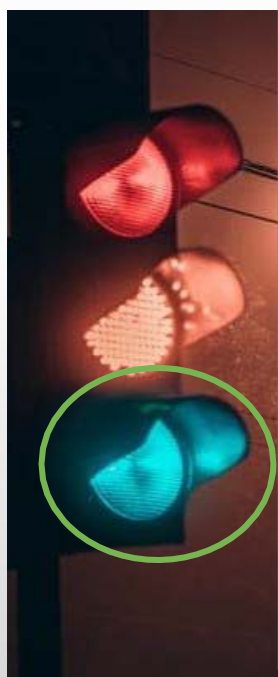
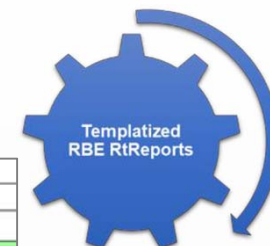
Path Forward: Review-by-Exception RtReports



Path Forward: Review-by-Exception RtReports

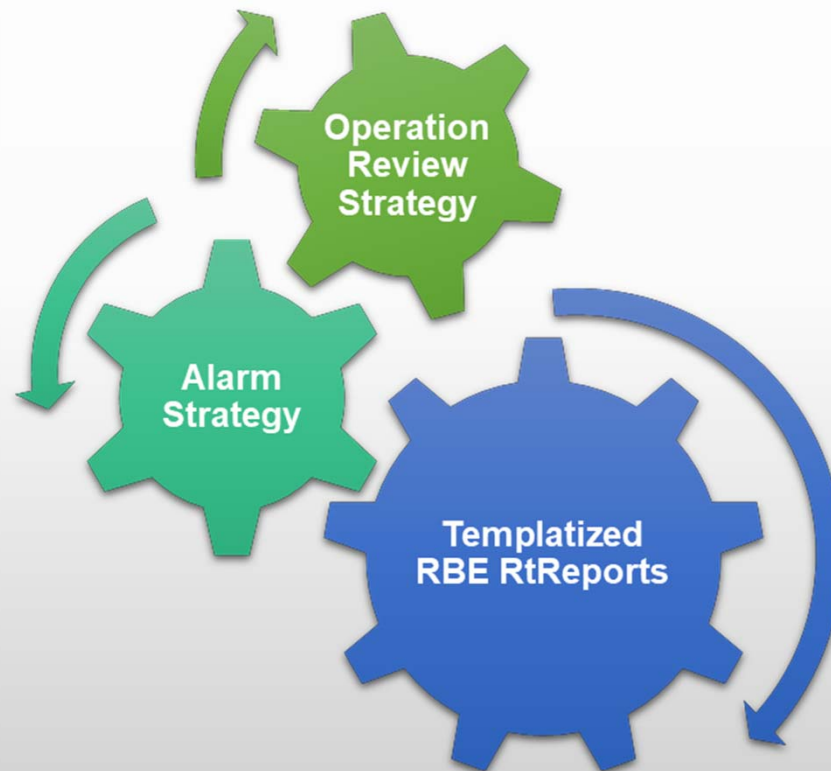


Path Forward: Review-by-Exception RtReports



Finding What Matters

Implementing Review-by-Exception RtReports
for Manufacturing at BioMarin

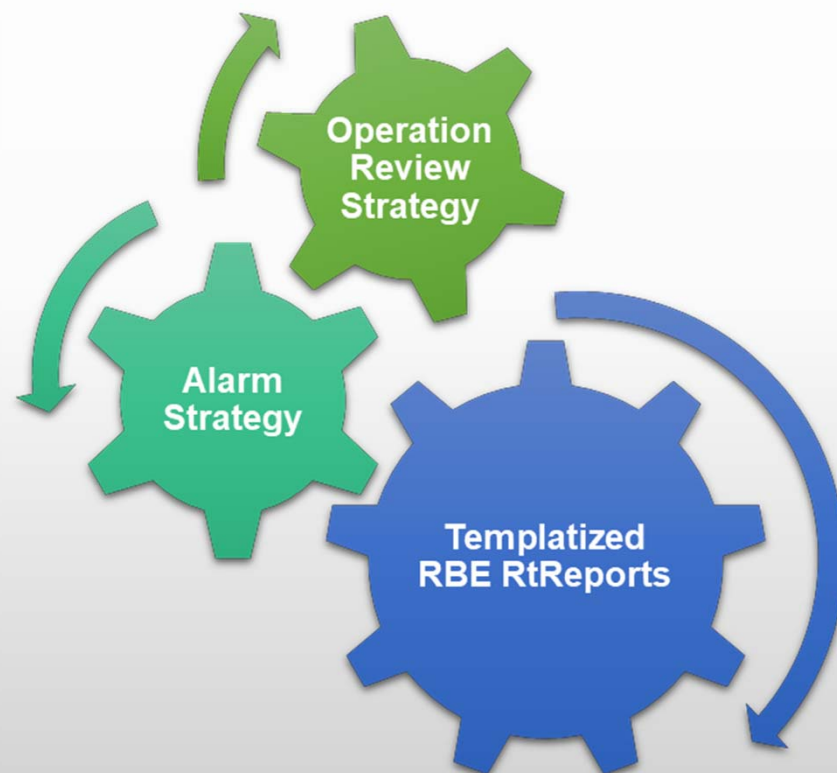


Finding What Matters

Implementing Review-by-Exception RtReports
for Manufacturing at BioMarin

Project Status

- Implemented:
 - Chromatography RBE RtReport
 - TFF RBE RtReport
- In Progress:
 - Alarm Strategy Updates
- Developing:
 - Bioreactor RBE RtReport

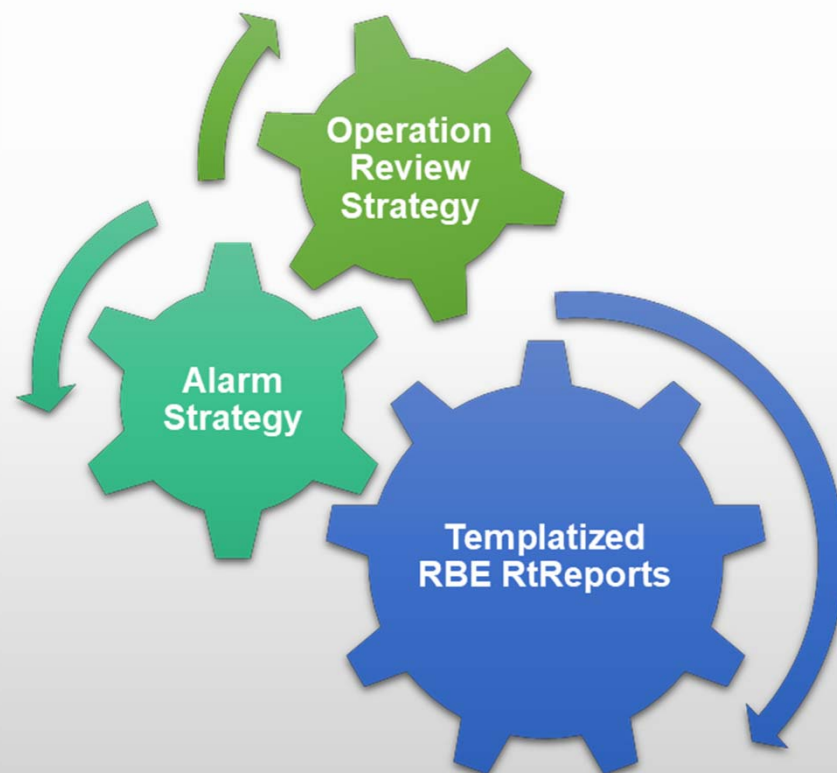


Finding What Matters

Implementing Review-by-Exception RtReports
for Manufacturing at BioMarin

Key Takeaways

- Defining exception candidates allows for focused scope
- Binary classifiers for exception events leads to a simplified report template
- Standardizing by equipment type eases qualification burden

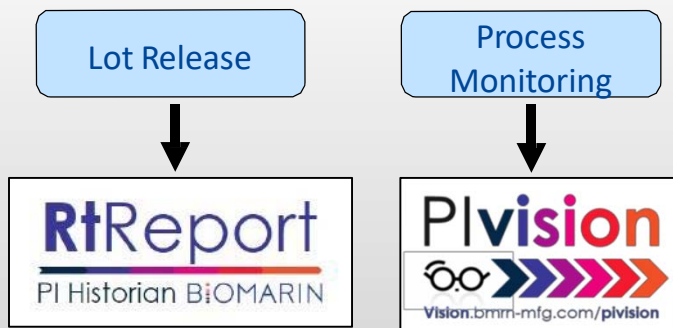


Finding What Matters

Implementing Review-by-Exception RtReports
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Next Steps

- PI Vision Event Frame displays for in-process exception monitoring
- RBE deployment for Bioreactors
- Multivariate online models with EFs



Finding What Matters

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BIOMARIN®

 OSIsoft.
PIWorld
THANK YOU

Questions?

Please wait for the
microphone

State your
name & company

