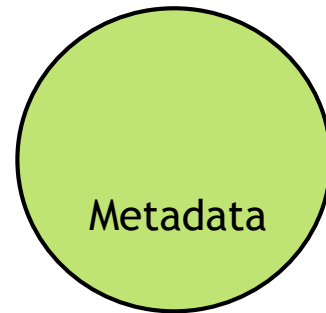


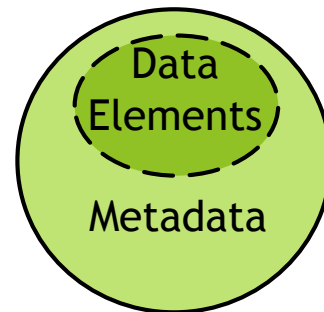
# Current Perspectives on Clinical Mass Spectrometry Auto-Data Review: An Innovative Solution

Alec Saitman, PhD DABCC (CC, TC)  
Director, Toxicology and Special Chemistry  
Providence Regional Laboratories

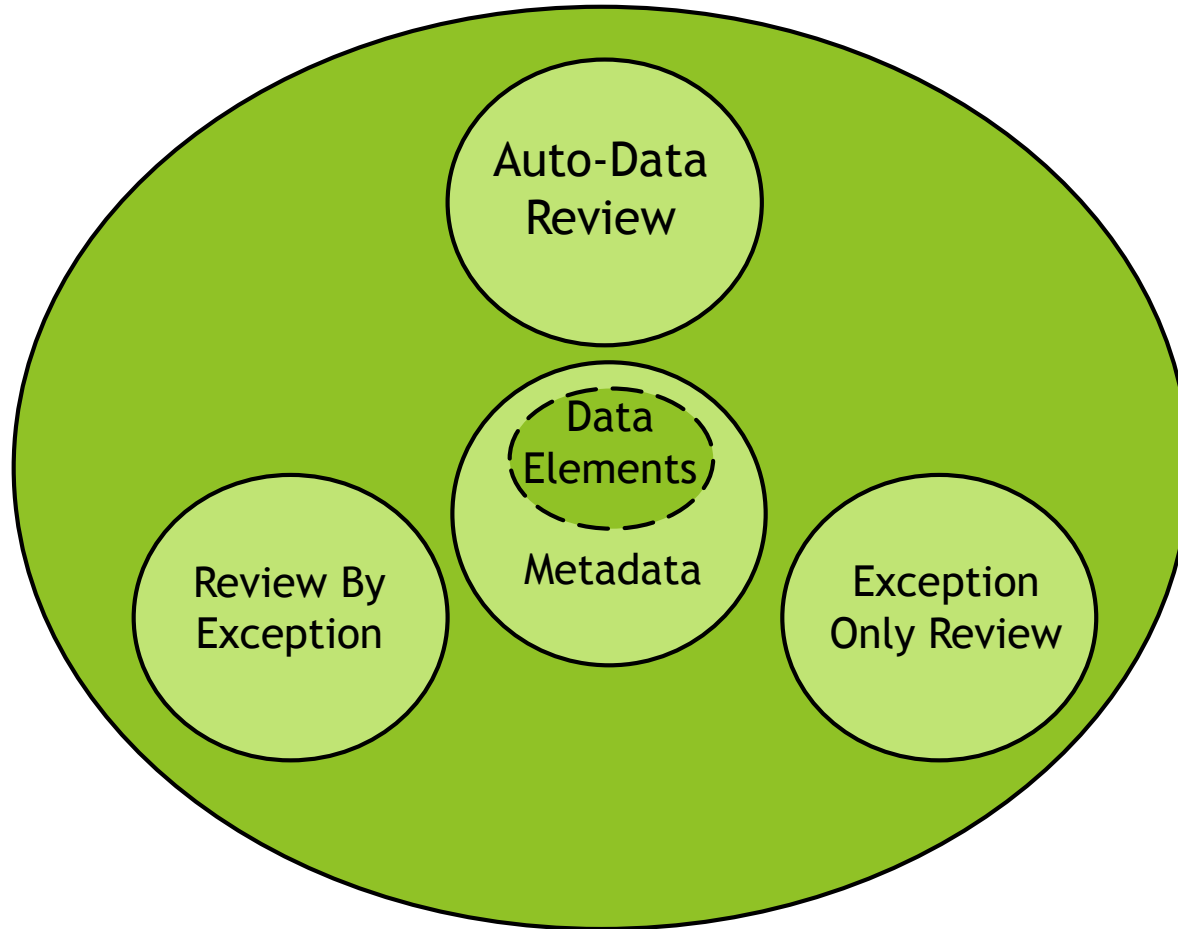
# Confusing Language



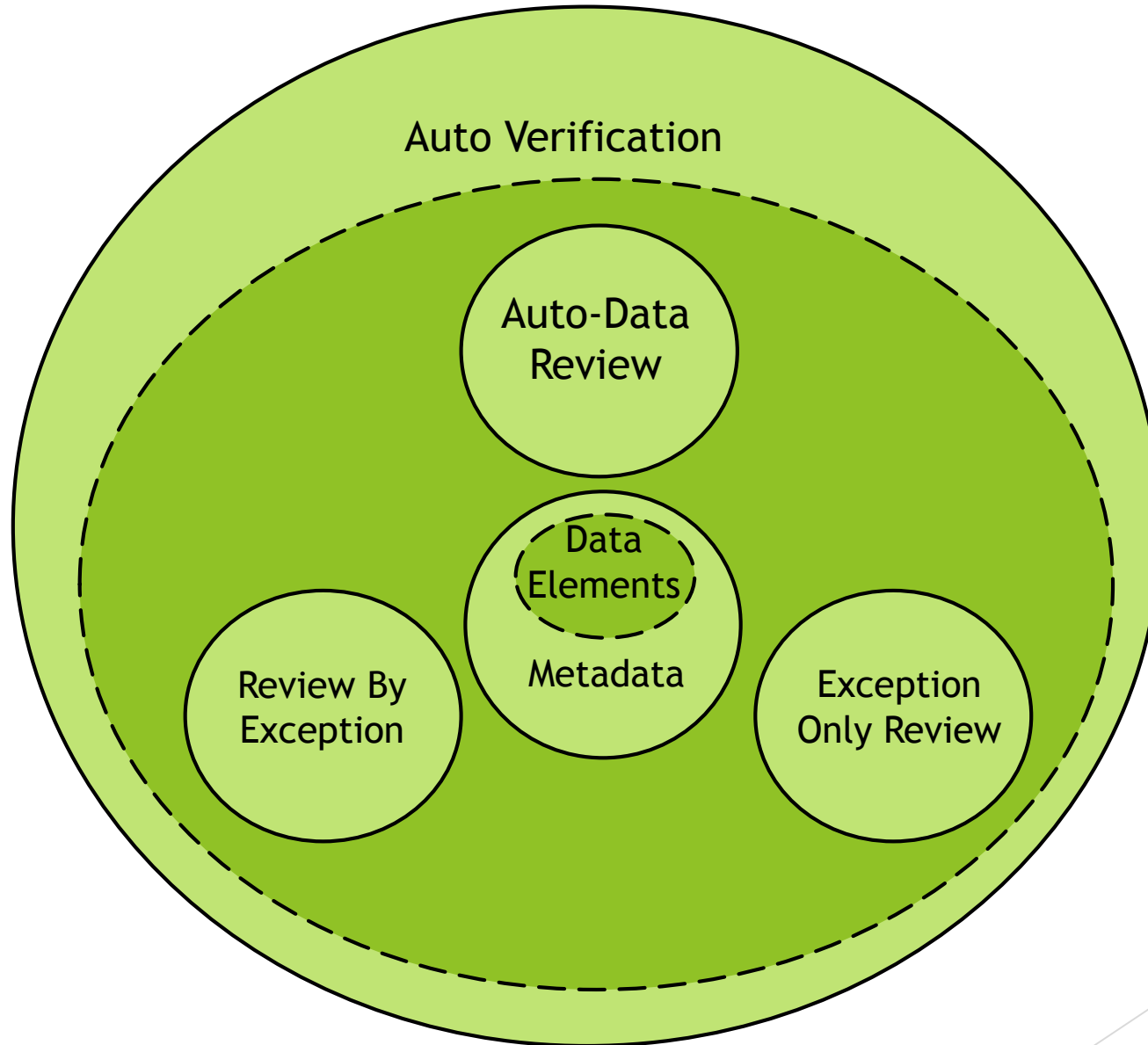
# Confusing Language



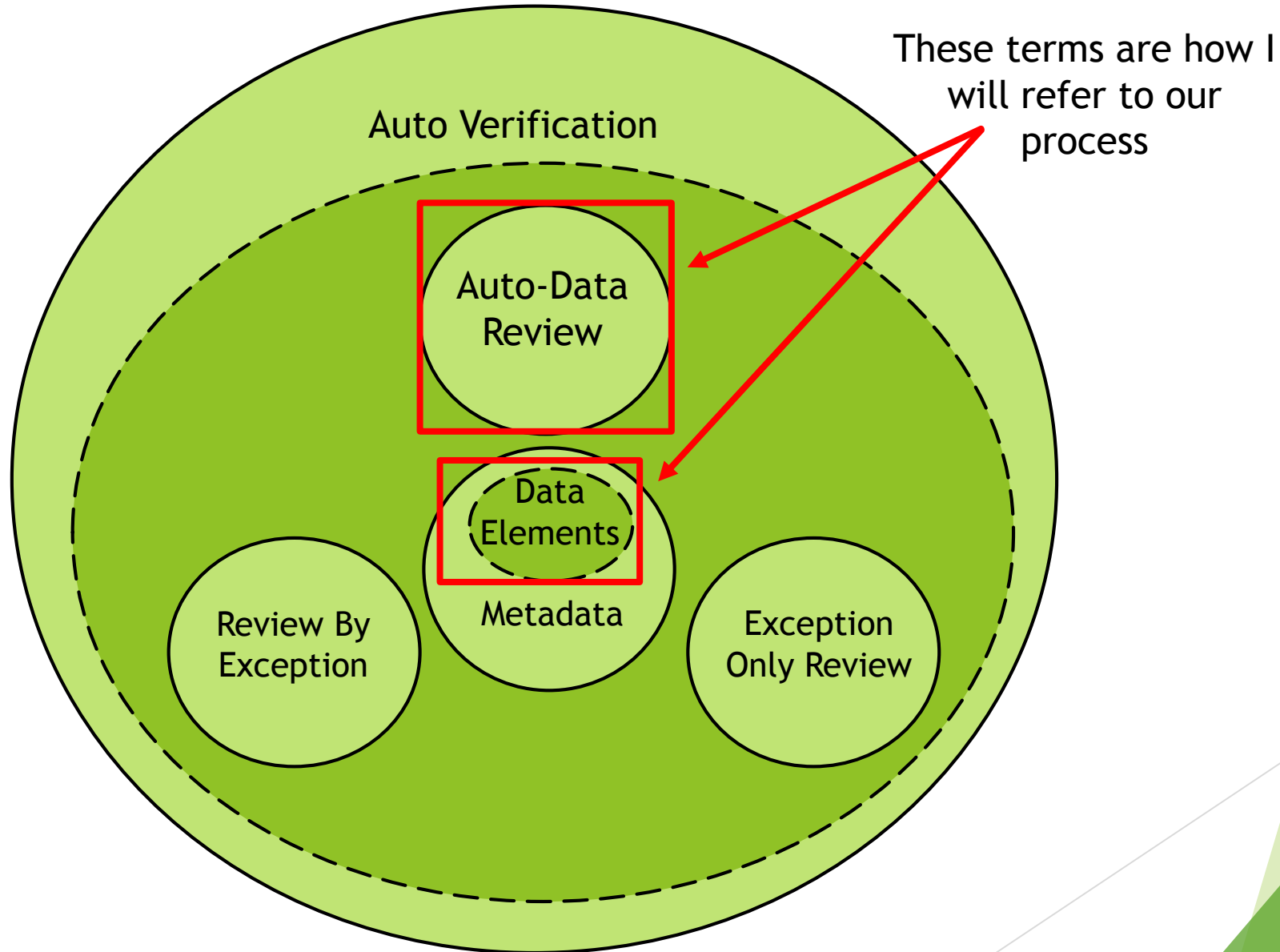
# Confusing Language



# Confusing Language



# Confusing Language



# Why Have an Automated Data Review Process for LC-MS/MS?

- ▶ Improve Efficiency (time)
- ▶ Reduce Errors
- ▶ Standardize Processes

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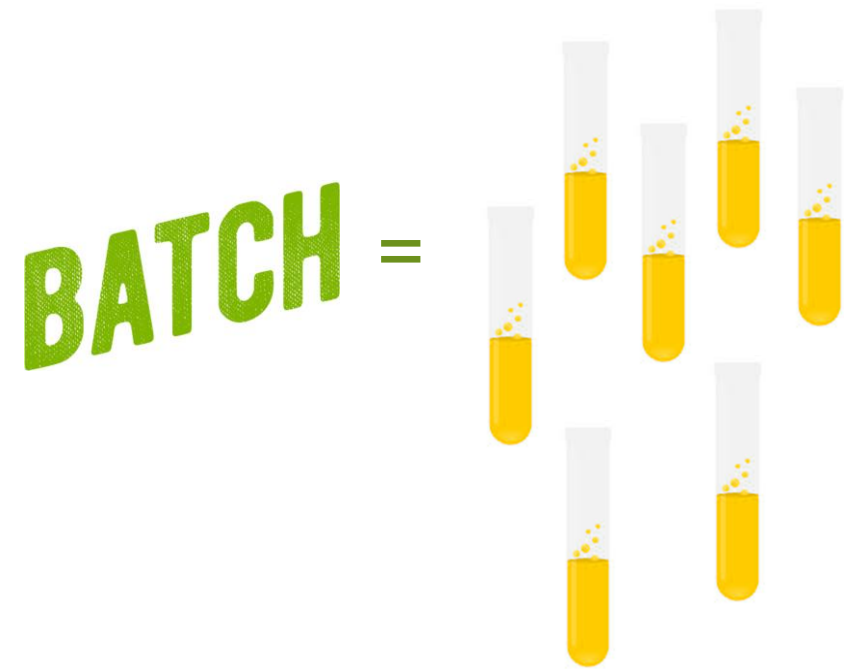
Because there are so many data elements to manually review!



# How Many Data Elements Need Manual Review in a Typical Mass Spectrometry Assay?

**BATCH**

# How Many Data Elements Need Manual Review in a Typical Mass Spectrometry Assay?



40 Samples  
Per Batch

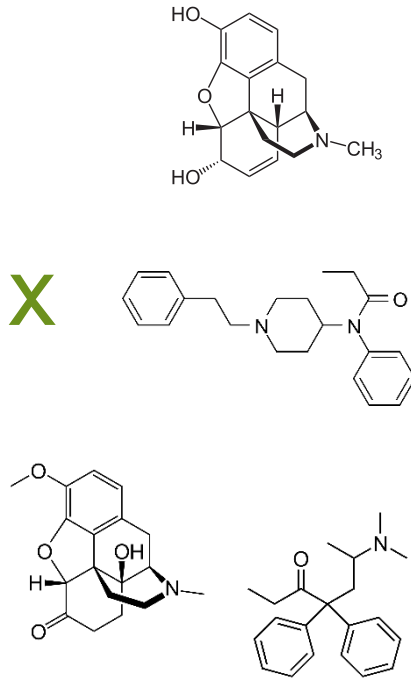
# How Many Data Elements Need Manual Review in a Typical Mass Spectrometry Assay?

**BATCH** =



40 Samples  
Per Batch

**X**



10 Analytes  
Per Sample

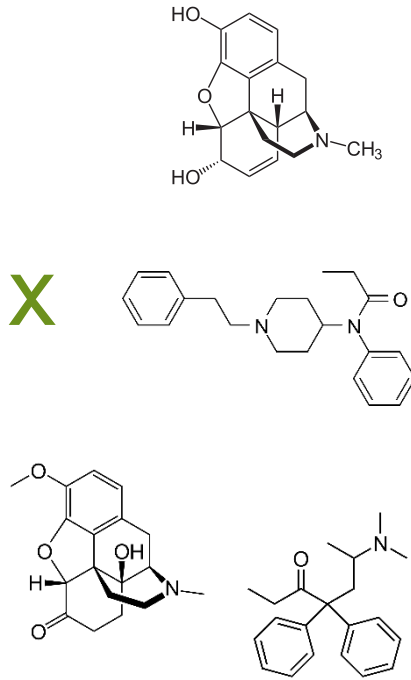
# How Many Data Elements Need Manual Review in a Typical Mass Spectrometry Assay?

**BATCH** =



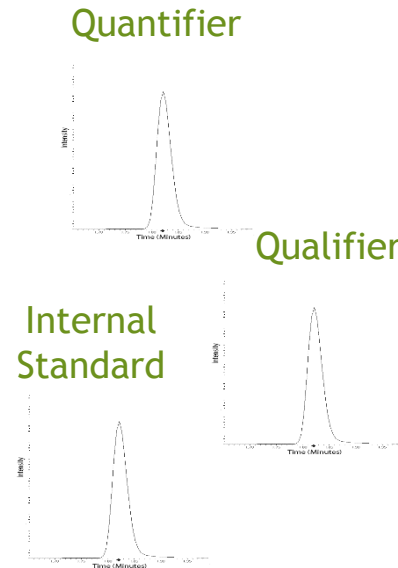
40 Samples  
Per Batch

X



10 Analytes  
Per Sample

X



3 Peaks Per  
Analyte

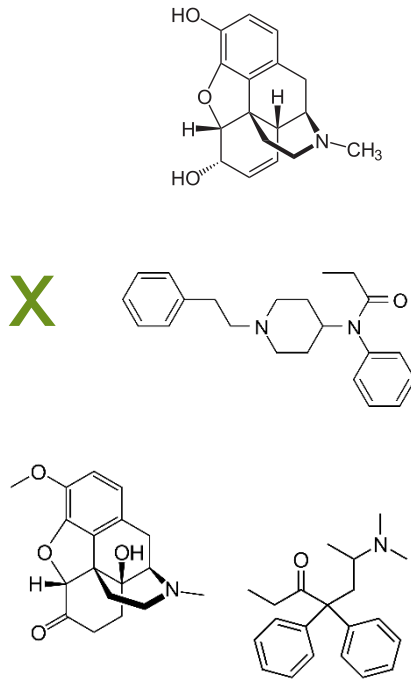
# How Many Data Elements Need Manual Review in a Typical Mass Spectrometry Assay?

**BATCH** =

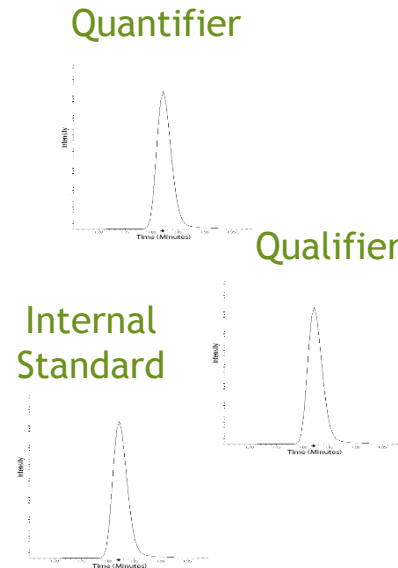


40 Samples  
Per Batch

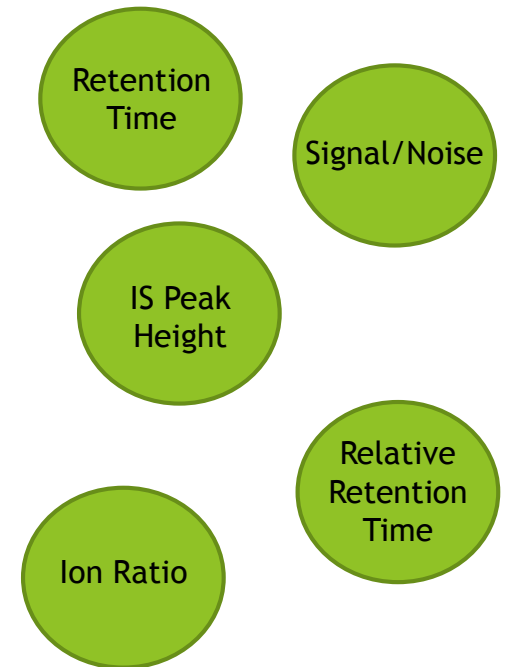
X



X



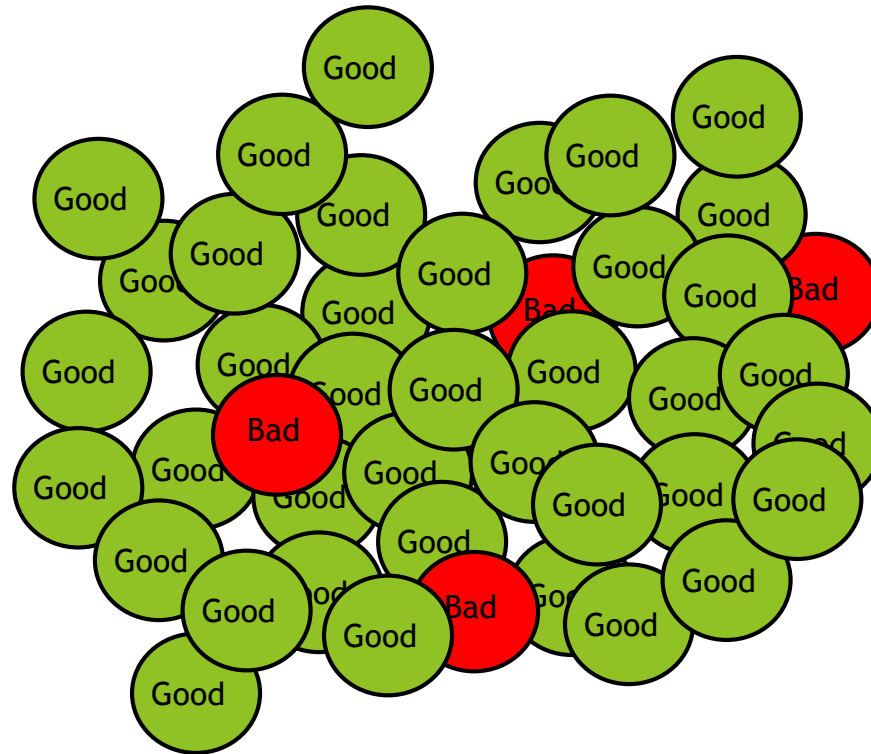
X



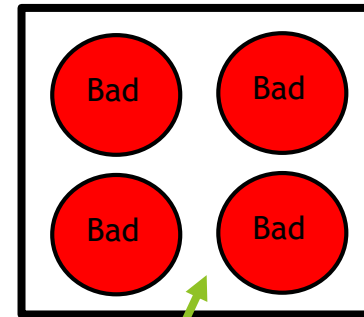
How Many Data Elements Need Manual Review in  
a Typical Mass Spectrometry Assay?

**BATCH** = 10,800 Data Elements To  
Manually Review!!!

# We Want to Filter the Jumble of Data



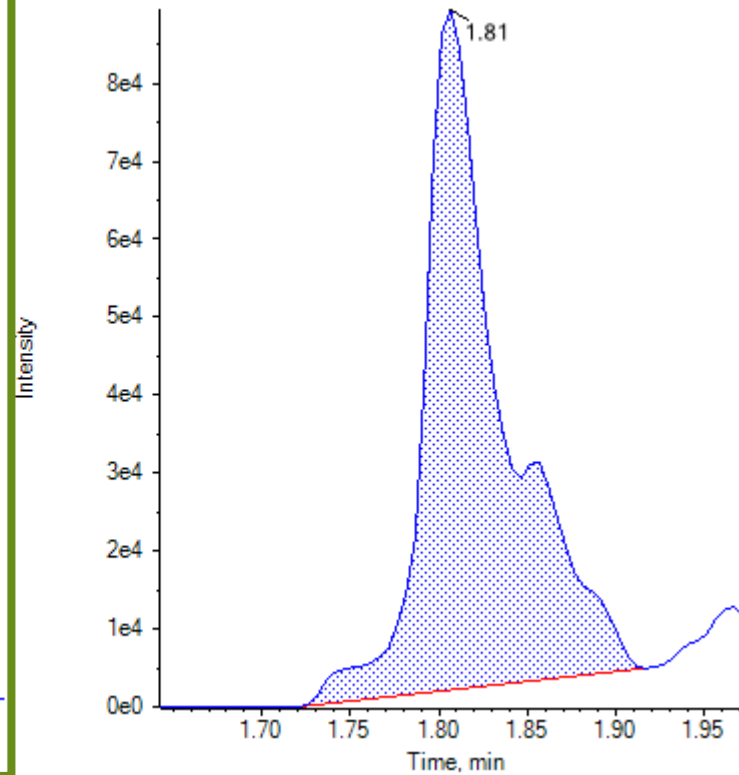
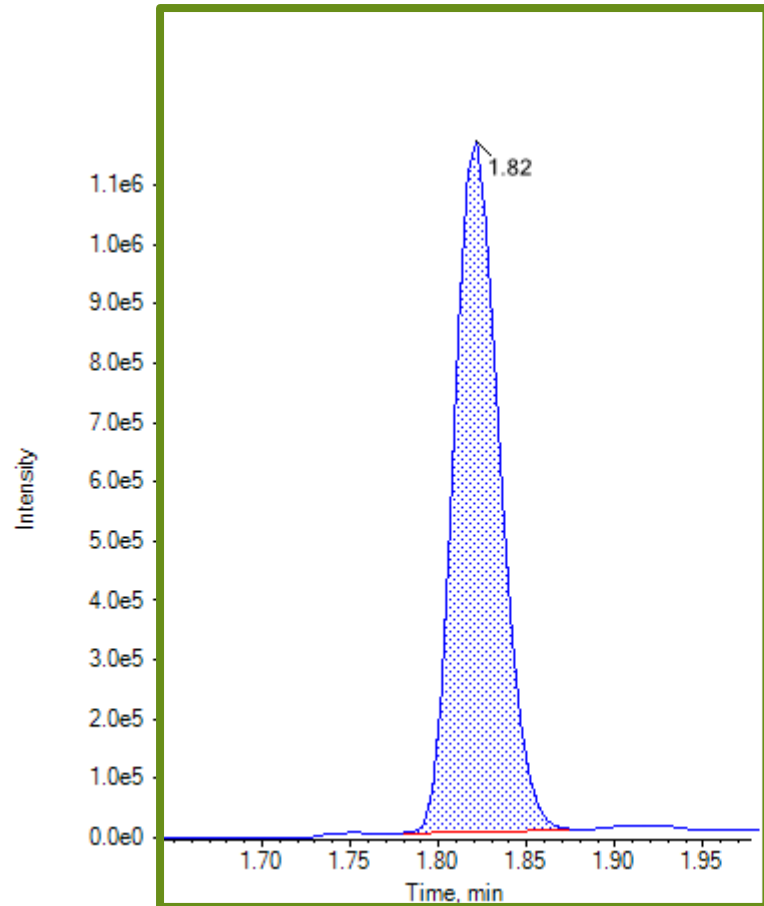
# To Focus on Only the Bad Data!



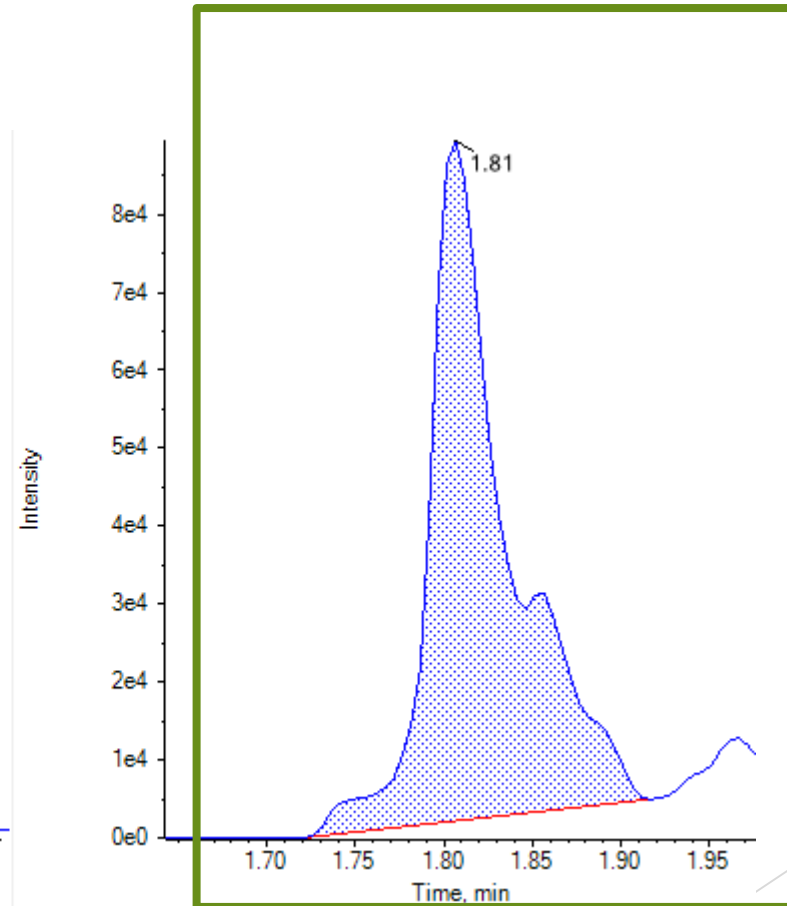
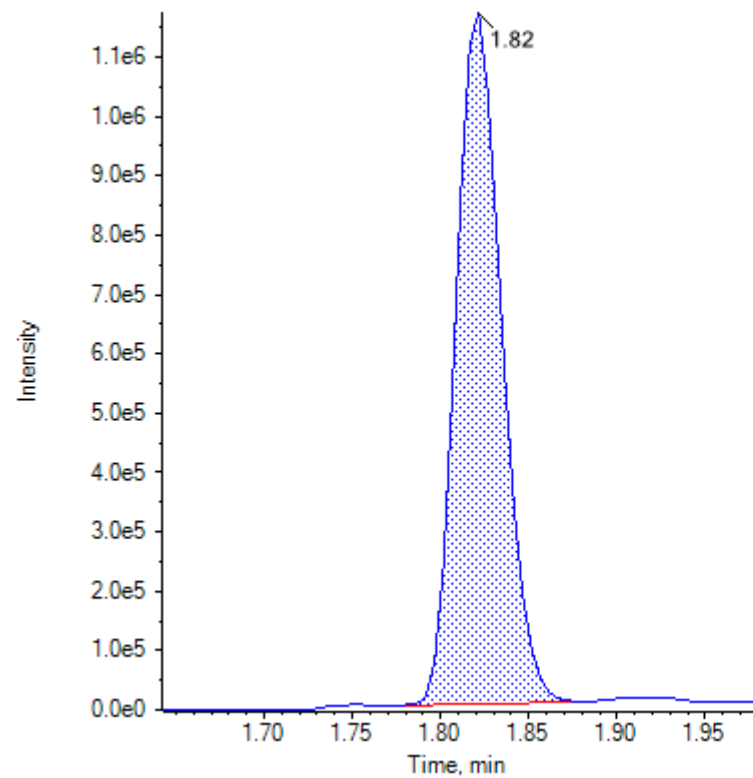
Isolate and Focus



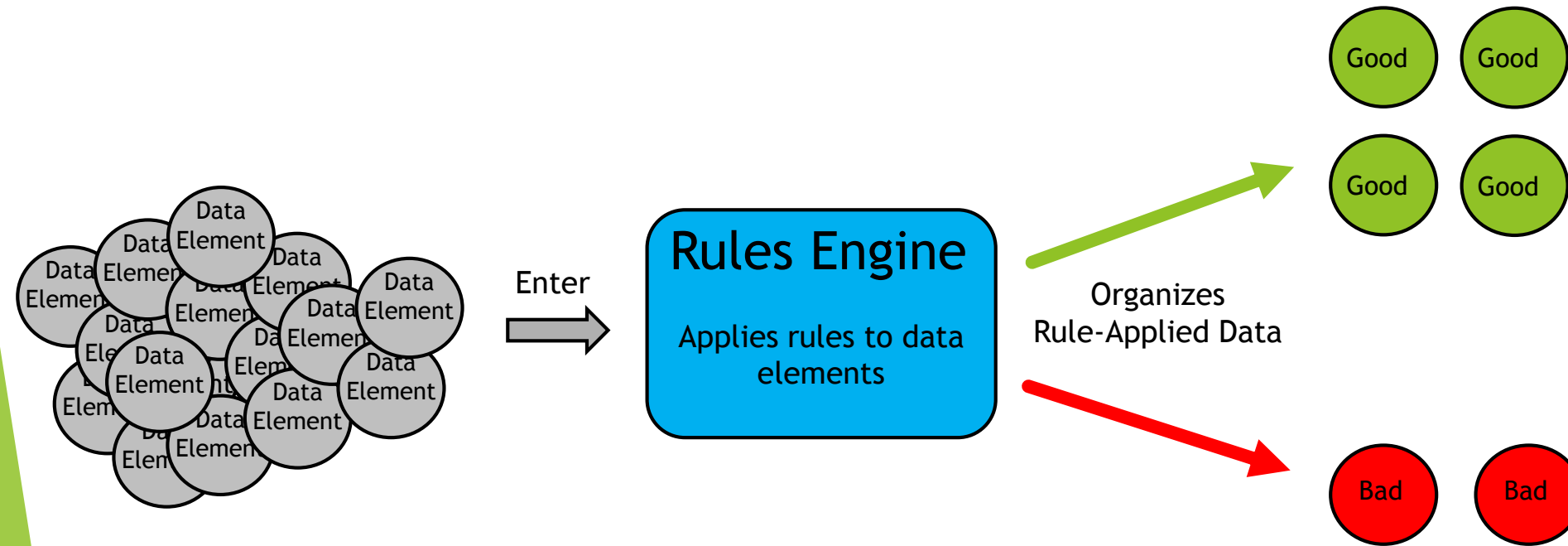
# We Want to Bypass This



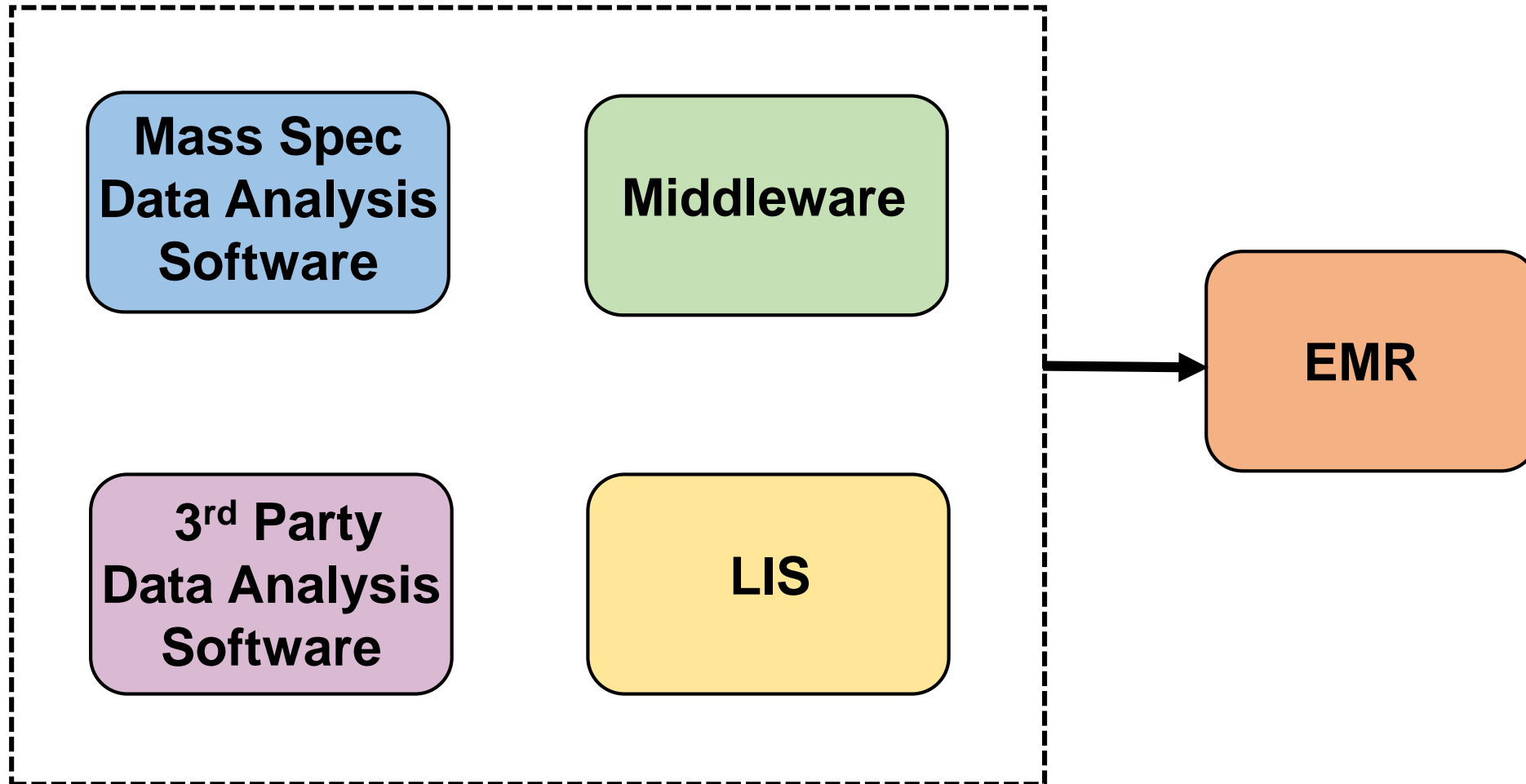
# But Capture This



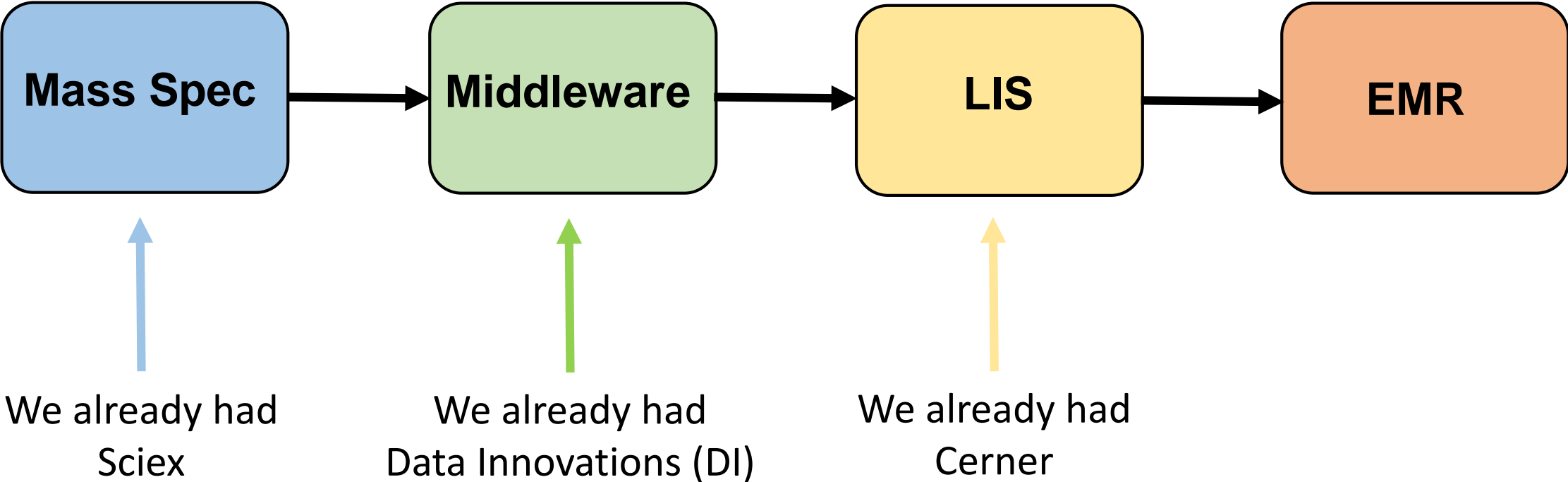
# This is Where a Rules Engine can Mitigate Manual Data Review



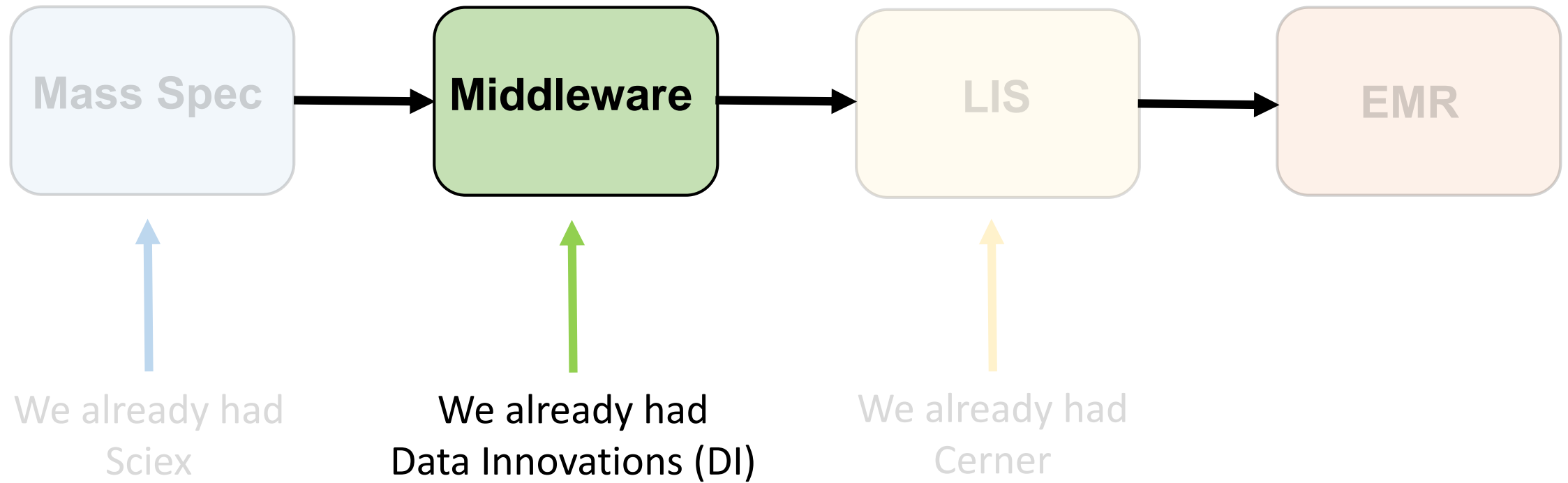
# Where Can a Rules Engine Live?



# This is Our Current Workflow



# This is Where the Rules Engine Placement Made Sense to Us



# Where We Started With DI

- ▶ Built rules based on static parameters
  - ▶ Different for each assay
  - ▶ Different for each analyte
  - ▶ Can not change over time

# But...it Gets Complicated...

- ▶ LC-MS/MS assays are dynamic processes
  - ▶ Data elements change and trend over time
- ▶ Rules with static values may/will eventually fail
- ▶ Requires constant monitoring and maintenance



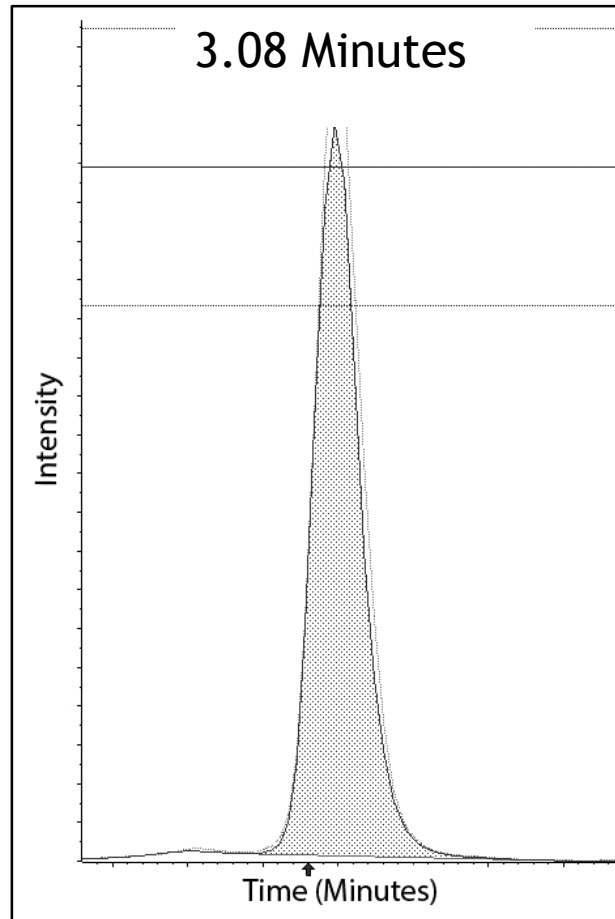
# Example of This Dynamic Process is Retention Time

- ▶ For Morphine

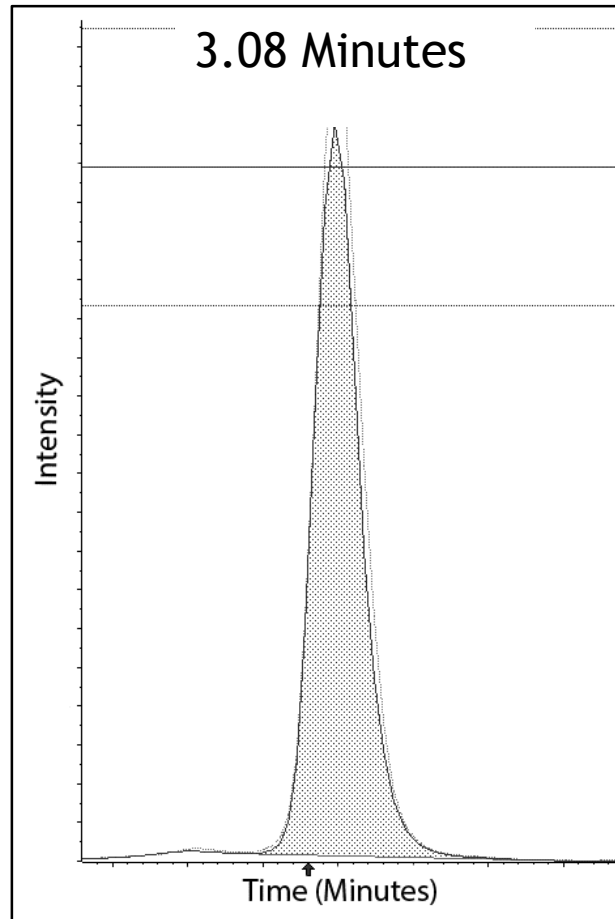
- ▶ A static rule is written

- ▶ If the morphine **Internal Standard Retention Time** is greater or less than 0.05 minutes from **3.08 minutes**, **then** flag the result as an outlier

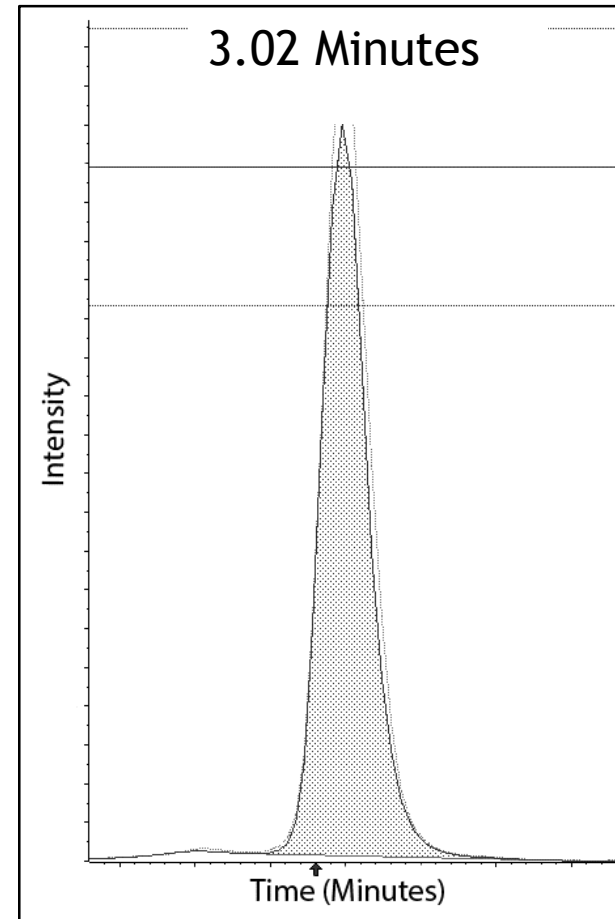

# Morphine Internal Standard Peak at Time of Rule Build



# 3 months later...Column is Replaced

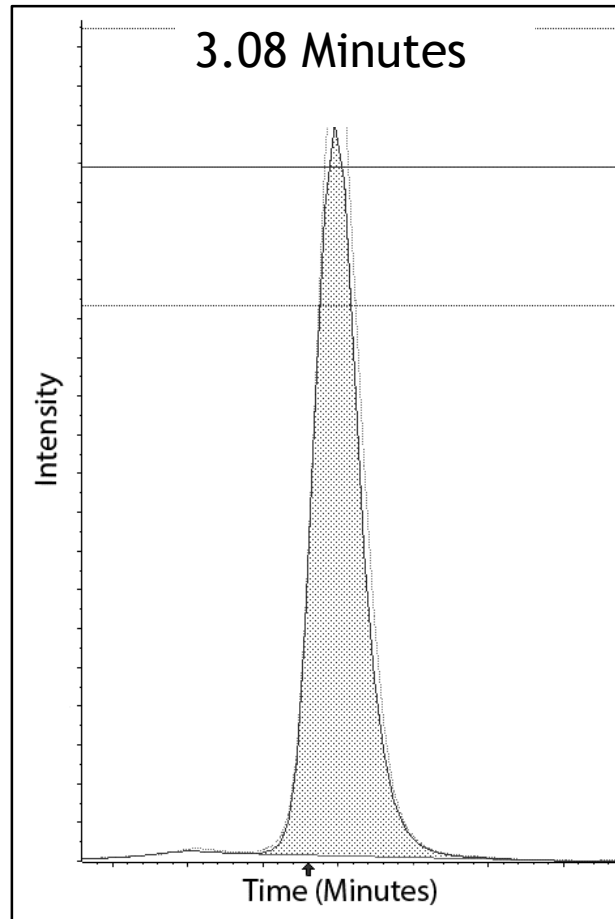


Retention  
Time Shift

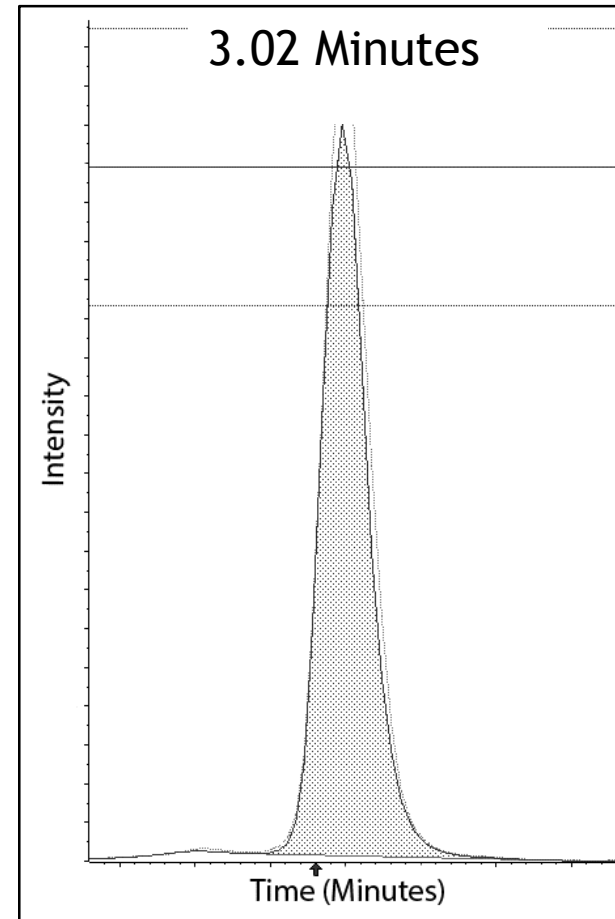


# 3 months later...Column is Replaced

All samples containing Morphine IS now fail that rule



Retention  
Time Shift



# What Could be Used to Generate Dynamic Rules?

- ▶ Calibrators! Because they calibrate more than just the value!



- ▶ Therefore the calibrators are intrinsically dynamic!

# What Could be Used to Generate Dynamic Rules?

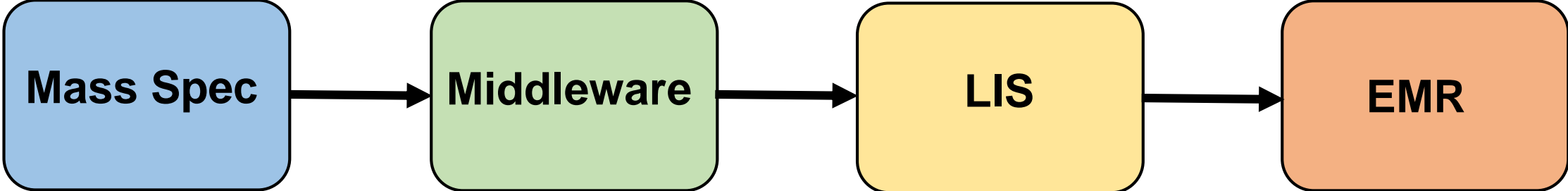
- ▶ Calibrators! Because they calibrate more than just the value!



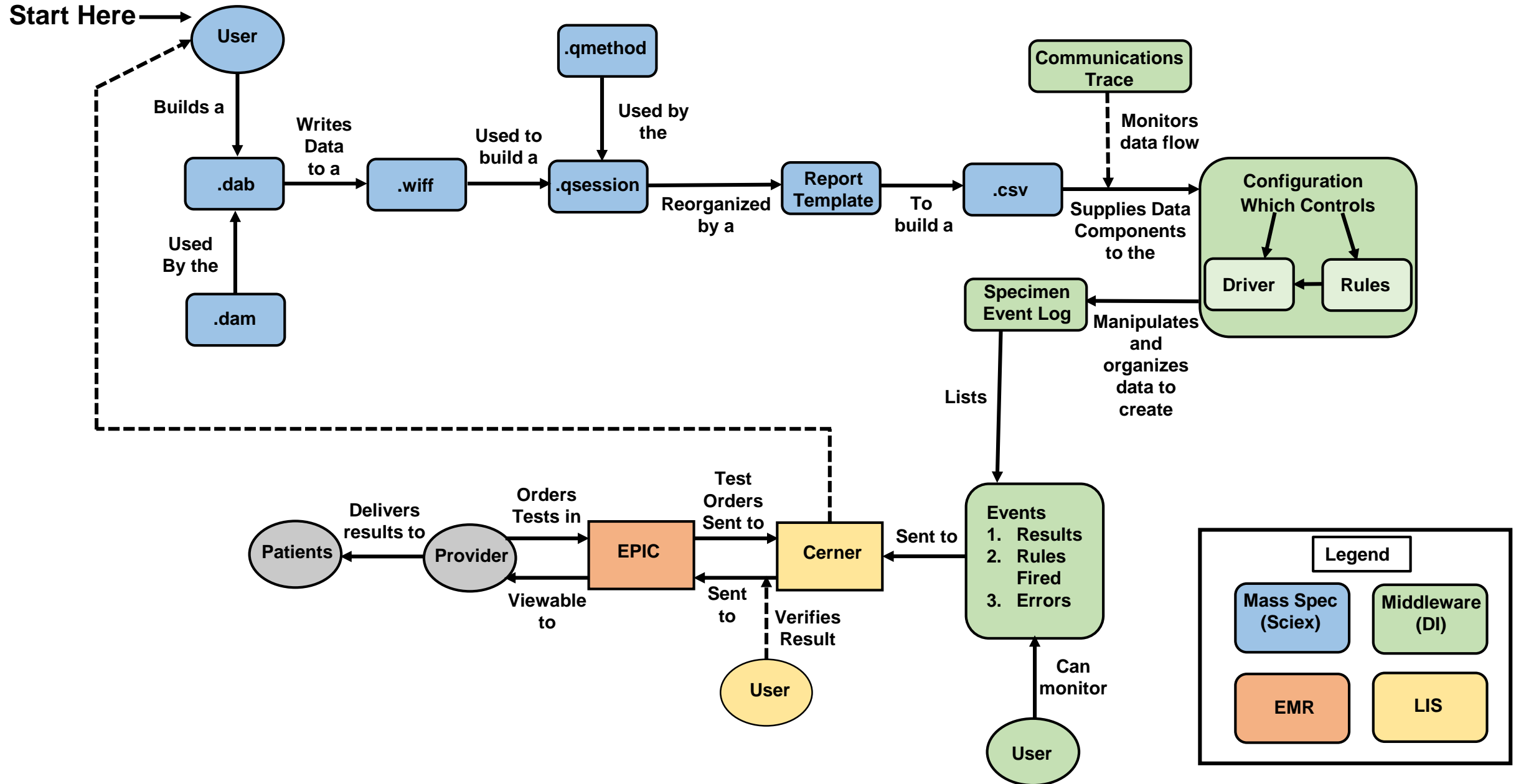
- ▶ Therefore the calibrators are intrinsically dynamic!

**We can capitalize on that!**  
**By averaging calibrator data elements!!**

# The Simple Workflow the End-User Sees

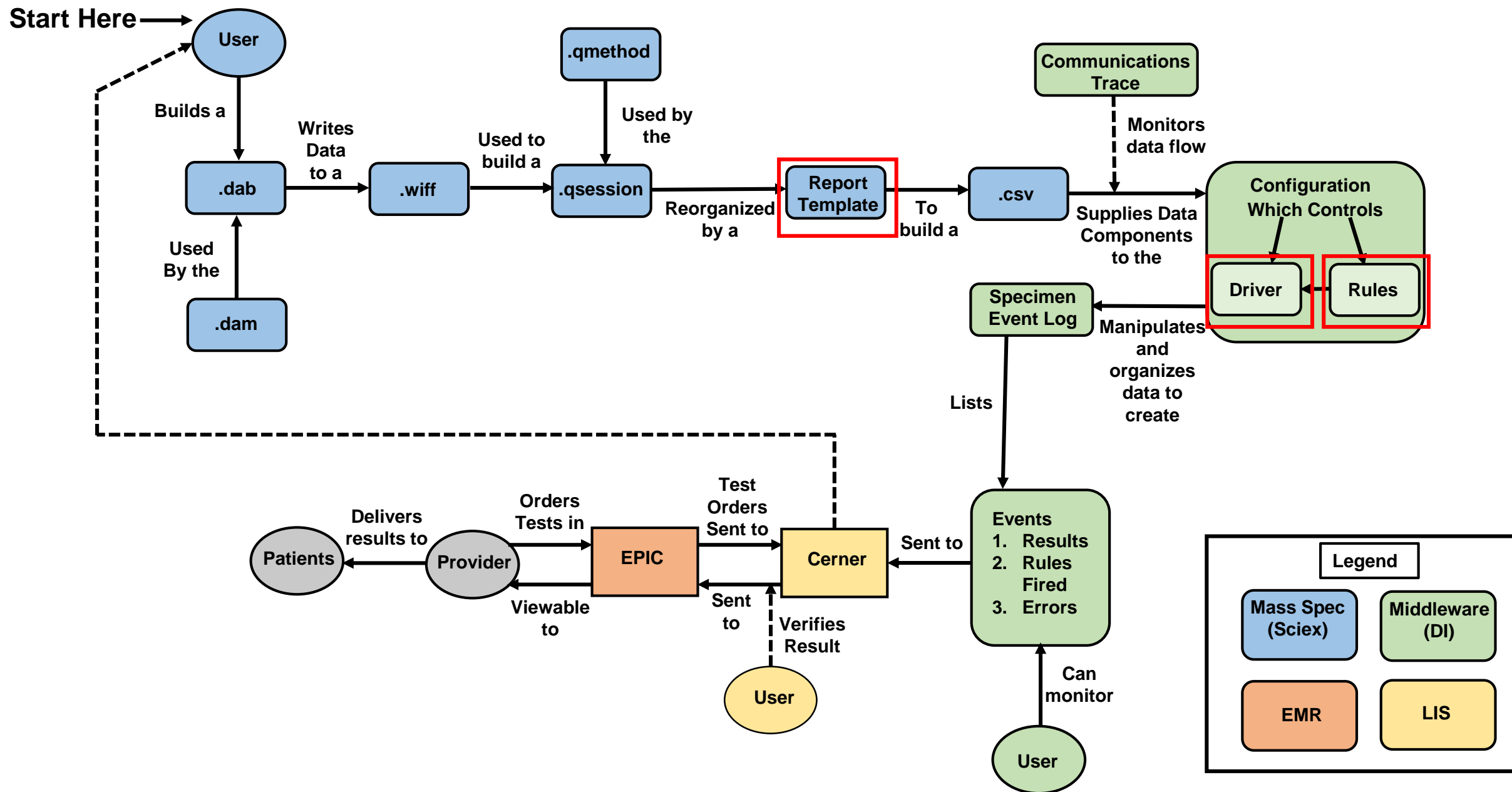


# What the “Behind the Scenes” Workflow Actually Looks Like!





# These are the 3 Components we Worked On



# Our To-Do List

Create a Report Template to send data elements to DI

Create a DI driver which can average data elements from calibrators

Have DI Driver place each calibrator data element average under each patient sample

Write and apply rules to patient samples

# What is a Report Template??

<Analyte

```
PeakName="Analyte Peak Name (PeakName)"
PeakArea="Analyte Peak Area (PeakArea)"
PeakHeight="Analyte Peak Height (PeakHeight)"
Concentration="Analyte Concentration (Concentration)"
CalculatedConcentration="Calculated Concentration (CalculatedConcentration)"
MRMAreaRatio="CUSTOM MRM Area Ratio (MRMAreaRatio)"
RetentionTime="Analyte Retention Time (RT)"
OutlierReasons="CUSTOM Outlier Reasons (OutlierReasons)"
SignalToNoise="Analyte Signal To Noise (SignalToNoise)"
RelativeRetentionTime="Calculated Relative Retention Time (RelativeRetentionTime)"
ExpectedMRMAreaRatio="CUSTOM Expected Ratio (ExpectedMRMAreaRatio)"
RecordModified="Run Script (RecordModified)"
>
</Analyte>
```

# Our To-Do List

Create a Report Template to send data elements to DI



Create a DI driver which can average data elements from calibrators

Have DI Driver list each calibrator data element average under each patient sample

Write and apply rules to patient samples

# What Exactly is a Driver?

- ▶ Part of DI Middleware
- ▶ Receives Data Elements
- ▶ Organizes Data Elements
- ▶ Applies Rules to Data Elements
- ▶ Flags Outlier Data Elements

# What Makes This Driver Special?

## ▶ OP CAL 1

- ▶ Morphine
  - ▶ Value 5 ng/mL
  - ▶ IS Retention Time 3.08

## ▶ OP CAL 3

- ▶ Morphine
  - ▶ Value 50 ng/mL
  - ▶ IS Retention Time 3.06

## ▶ OP CAL 2

- ▶ Morphine
  - ▶ Value 10 ng/mL
  - ▶ IS Retention Time 3.07

## ▶ OP CAL 4

- ▶ Morphine
  - ▶ Value 100 ng/mL
  - ▶ IS Retention Time 3.07

# What Makes This Driver Special?

## ▶ Patient 1

### ▶ Morphine

- ▶ Value 56 ng/mL
- ▶ IS Retention Time 3.15
- ▶ Average Calibrator IS Retention time 3.07

## ▶ Patient 2

### ▶ Morphine

- ▶ Value 582 ng/mL
- ▶ IS Retention Time 3.07
- ▶ Average Calibrator IS Retention time 3.07

# Our To-Do List

Create a Report Template to send data elements to DI ✓

Create a DI driver which can average data elements from calibrators ✓

Have DI Driver place each calibrator data element average under each patient sample ✓

Write and apply rules to patient samples



# An Example Rule we Wrote

- ▶ Internal Standard Retention Time for Morphine:
  - ▶ If the morphine **Internal Standard Retention Time** is greater or less than 0.05 minutes of the **average of the calibrators** for morphine, **then** flag the result as an outlier
- ▶ 30 rules in total...and growing!

# How does a Bench Tech See a Result?

The screenshot displays a software interface for a laboratory information system. The main window is titled "Toxicology Workspace" and contains two primary panels: "Specimen Worksheet" and "Run Worksheet".

The "Specimen Worksheet" panel on the left contains a table with the following data:

Specimen ID	Position	Patient Name
01108639A	11	
01107288A	12	
01209570A	13	
01213916A	16	
▶ 01213094A	17	
01209305A	20	
01115382A	21	
01214817A	26	
01215082A	30	

The "Run Worksheet" panel on the right displays a table of test results for the selected specimen (01213094A):

Test Name	Error Code(s) (1)	Result (1)	Test Status (1)	Result Date/Time (1)	Test Instrument I...
▶ - (none)					
OP Hydrocodone 1	. IS Retention Time	84.73	Held for Verification	1/17/2018 1:53:12 PM	C Chem Sciex 01
OP Oxycodone 1	Saturation	3720.70	Held for Verification	1/17/2018 1:53:12 PM	C Chem Sciex 01
OP Oxycodone 2	Saturation	3804.08	Held for Verification	1/17/2018 1:53:12 PM	C Chem Sciex 01

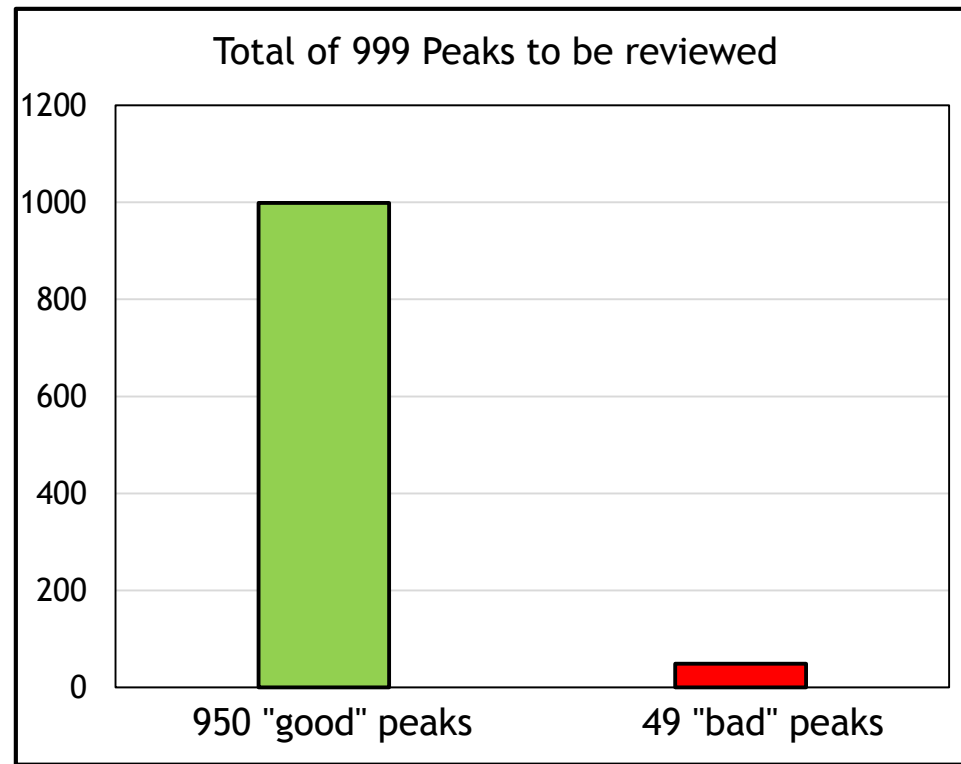
Green boxes highlight the selected specimen row in the Specimen Worksheet and the corresponding test results in the Run Worksheet.

# How are we Validating?

- ▶ Made all rules fire at least once
  - ▶ Not an easy task!
- ▶ Tried combinations of rule firing
- ▶ Analyzed multiple production patient batches both manually and by DI
  - ▶ Compared results and time

# The Data

- ▶ Typical batches take about 2.5 hours to manually review
- ▶ A Real Opiate Batch with 37 patients was analyzed on 1/15/2018
- ▶ Batch Reviewed both:
  - ▶ Manually
  - ▶ Auto Data Review



- ▶ Both manual and auto data review found the exact same 49 “bad” peaks
- ▶ Estimated time to review cut by 50 %
  - ▶ Anticipated time to review will be only 20% of manual review.

# Questions? Caveats?

- ▶ Is this solution in production in your lab?
- ▶ Is this a “plug and play” solution?
- ▶ Is the driver from DI you use, available?
- ▶ What is next?

**More to Come! I Promise!**

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Providence Regional Laboratories  
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