Quotient Sciences

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When things go wrong: Normalising failure

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To Err is Human

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Failure is an aspect of everyday life

At sometime, somewhere, we have or will, all fail at something

Preconceptions of failure

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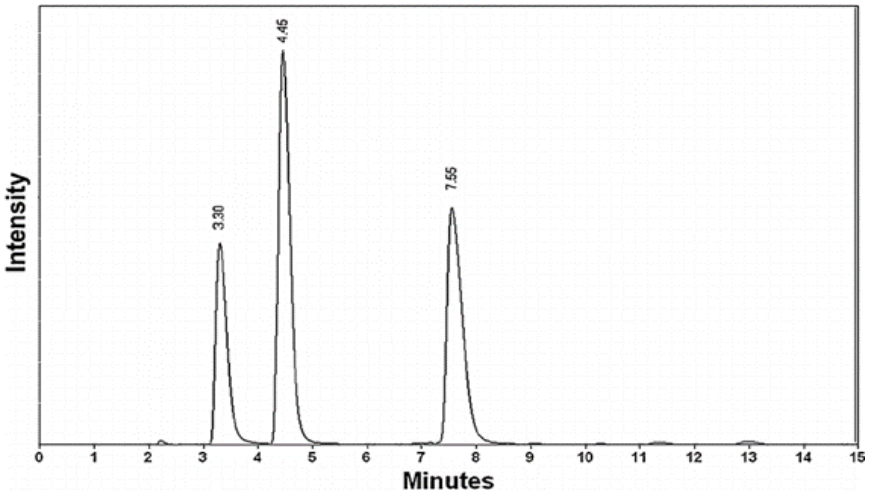
As you'd expect, failure has typically negative connotations around it

Societal pressure, in all forms, pushes for (or at least the appearance of) success



The importance of failure

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It is a critical part of the learning process, and a stepping stone to long term success

By taking the time to understand <u>why</u> something failed, we can gleam useful information that can:

- **Lead to personal growth, and increased resilience**
- **The later success/optimisation of the process**
- **Contribute to the greater understanding of the given field for others to build on**
- **Gain experience and knowledge**

Normalising failure

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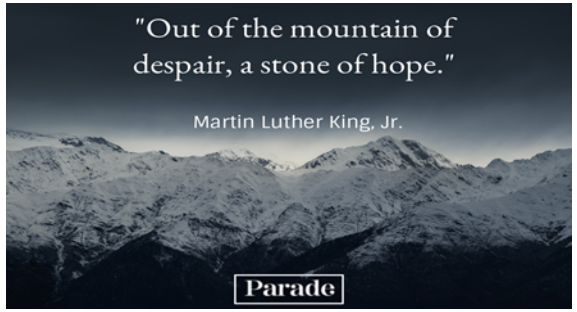
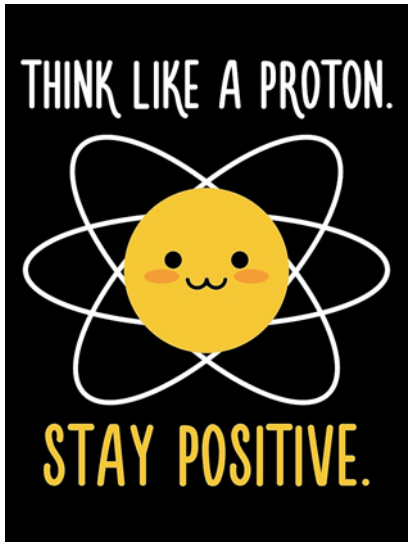
We all know this of course, we are surrounded by inspirational sayings of some form





However this doesn't mean we readily admit or publicise our failures

As young scientists it is important we accept and normalise failure, openly discuss it, and our results, for the continued development of bioanalysis

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But how do we understand failure?

Understanding failure

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Root cause analysis is an important and powerful tool in which to understand failure and find/implement a solution

The usual five steps in RCA are:

- Define the problem

- Gather data on the problem

- Identify causal factors

- Determine the root cause(s)

- Recommend and implement solutions

Though there are variations on these, the aim remains the same

Root cause analysis

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RCA is not a single well defined method however, and there are a variety of different processes designed to compliment different areas such as:

- **Safety**
- **Production**
- **Process**
- **Equipment failure**
- **Systems**

So what are some of the RCA methods that can compliment bioanalytical work?

Root cause analysis methods

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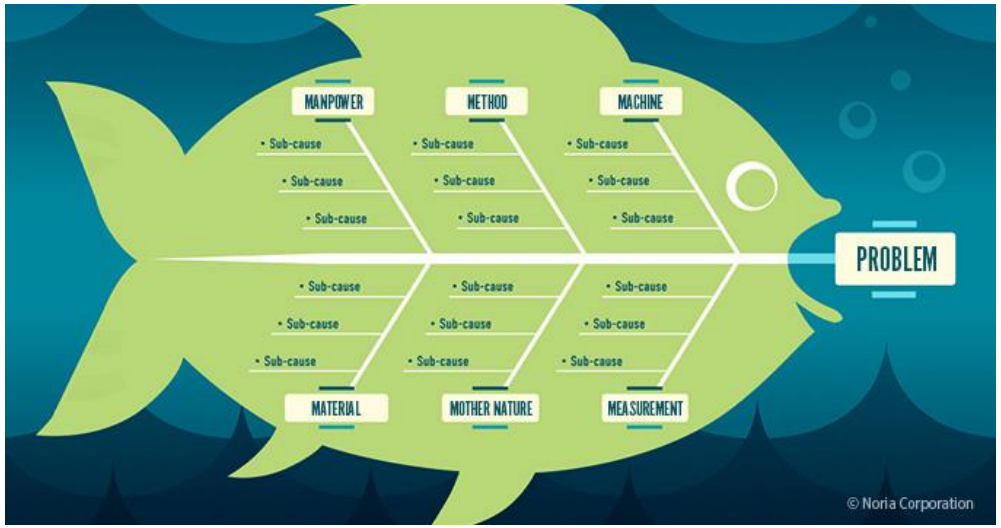
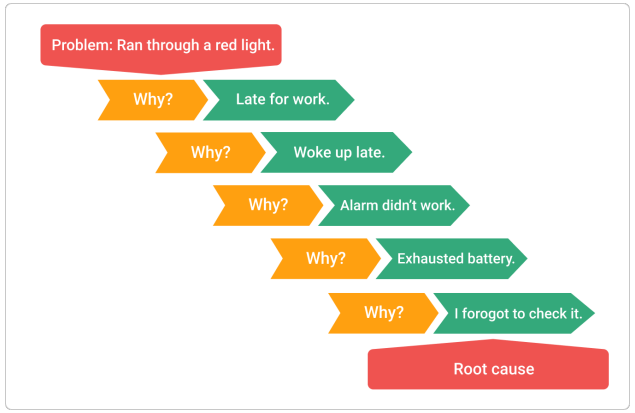
Some common RCA methods include:

- Ishikawa/fishbone diagram
- Five why
- Cause and effect analysis
- Logic tree



Most of these methods make use of universal structures, such as flowcharts, tree diagrams, pareto charts and brainstorming sessions



Each of these methods comes with its own advantages and disadvantages depending on context of use, so careful selection is important

What does failure look like in bioanalysis, in the context of chromatography?

What failure can look like in Chromatography

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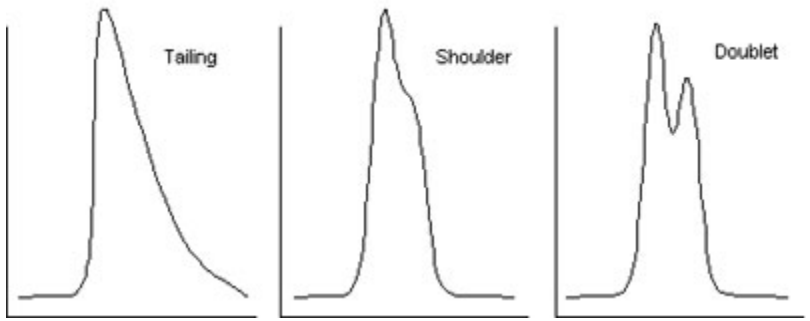
In chromatography failure can seen in multiple forms, such as:

- Poor shape / split peaks
- Variability with extraction recovery / matrix effect
- Sudden issues with the assay/equipment breakdowns
- Incorrect solution preparation
- Contamination



Causes of these failures can vary significantly from something as simple as an error by an analyst to serious issues in method transfer documentation

Use of RCA methods, allows efficient and quick understanding of the actual/potential reason for the failure, and by extension aid in the implementation of an effective solution

RCA in action – A case study

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To help illustrate the use of RCA to determine a point of failure, we will look at a case study of it in use

In this case study, test and reference article samples prepared for a validation, from solutions provided by a client, have repeatedly come back higher than the nominal concentration expected, but consistently have a good %CV. i.e. good precision, poor accuracy

A fishbone diagram was used early on to get an overall picture of the causes that could result in the failure of the assays accuracy

Case study – A birds eye view

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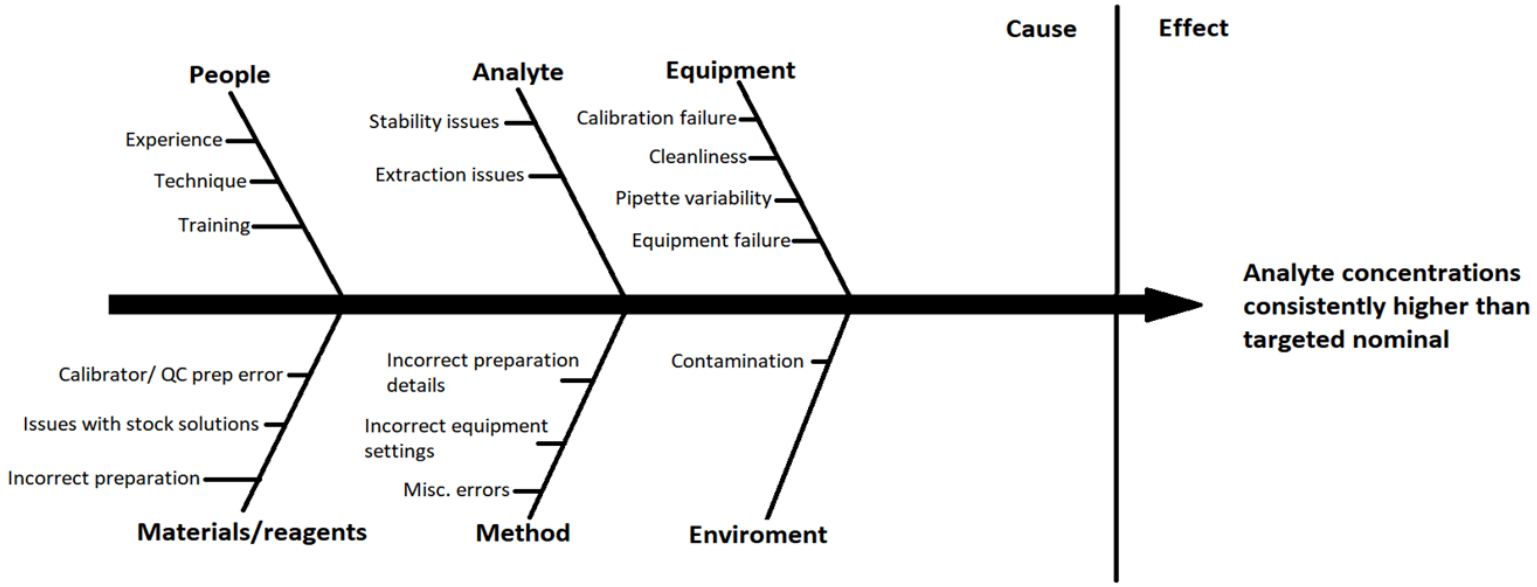
The following fishbone diagram was drafted up to give an overall picture on all of the potential causes to why the nominal concentrations could not be achieved



A process of elimination was used to remove causes (from most to least likely) and evidence of each eliminated cause noted down.

Case study – Initial elimination of causes

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People (experience & training)

- Experienced senior analyst with a decade of experience

Training & experience unlikely

Equipment (calibration failure, pipette variability, cleanliness & equipment failure)

- Pipettes were verified both externally and internally before use
- Good CV% indicative of low variability in extraction process
- Analytical system functioning as expected, tuned successfully and within acceptance
- Analytical system passed its system suitability test

These make it very unlikely to be calibration & equipment failure, cleanliness and pipette variability

Case study – Initial elimination of causes 2

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Method (incorrect preparation details, incorrect equipment settings, Misc. errors.

- Analytical specification goes through QC process before sign off, checked again to be sure and no errors found

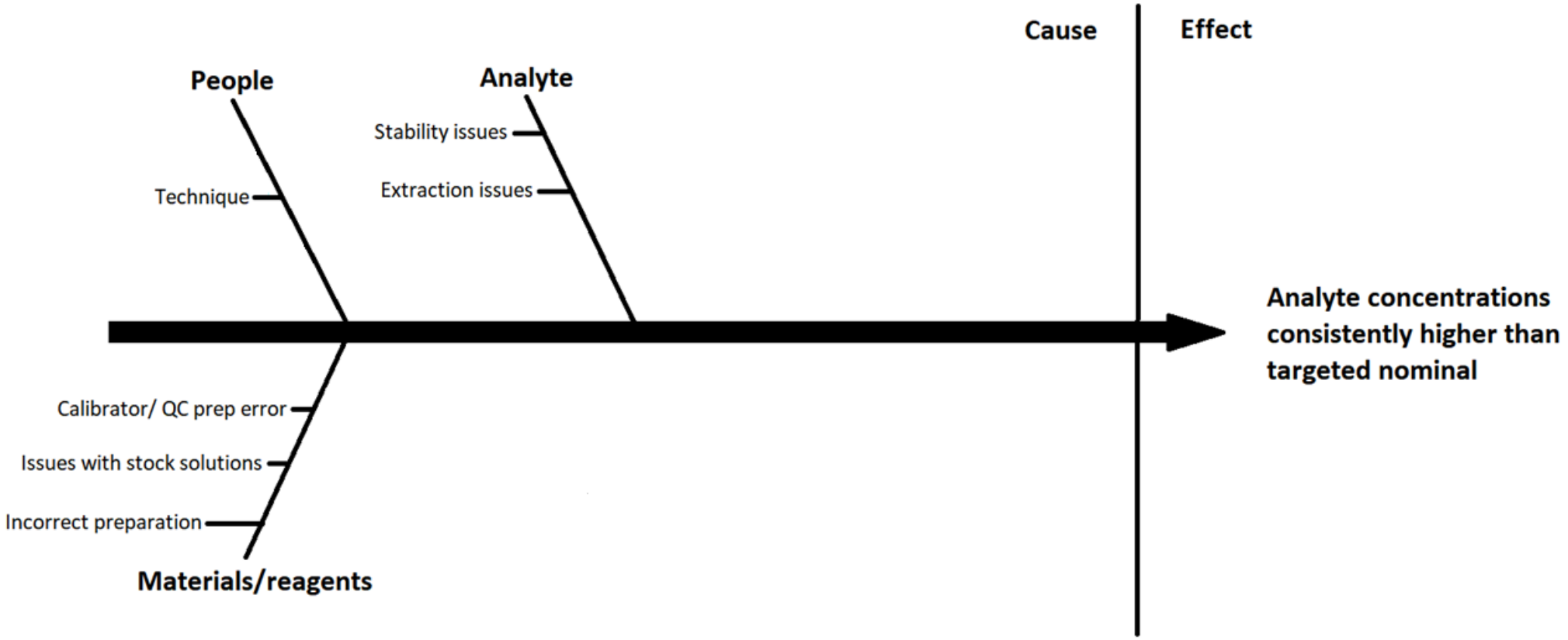
Unlikely to be a method specification issue

Environment (contamination)

- Lab used for trace element analysis, as such the laboratory and cabinets are routinely cleaned
- In analytical runs, calibrators, QCs, and blanks have shown no sign of contamination

As such environmental contamination is unlikely

Case study – Cause overview 2



Case study – Consideration to the analyte

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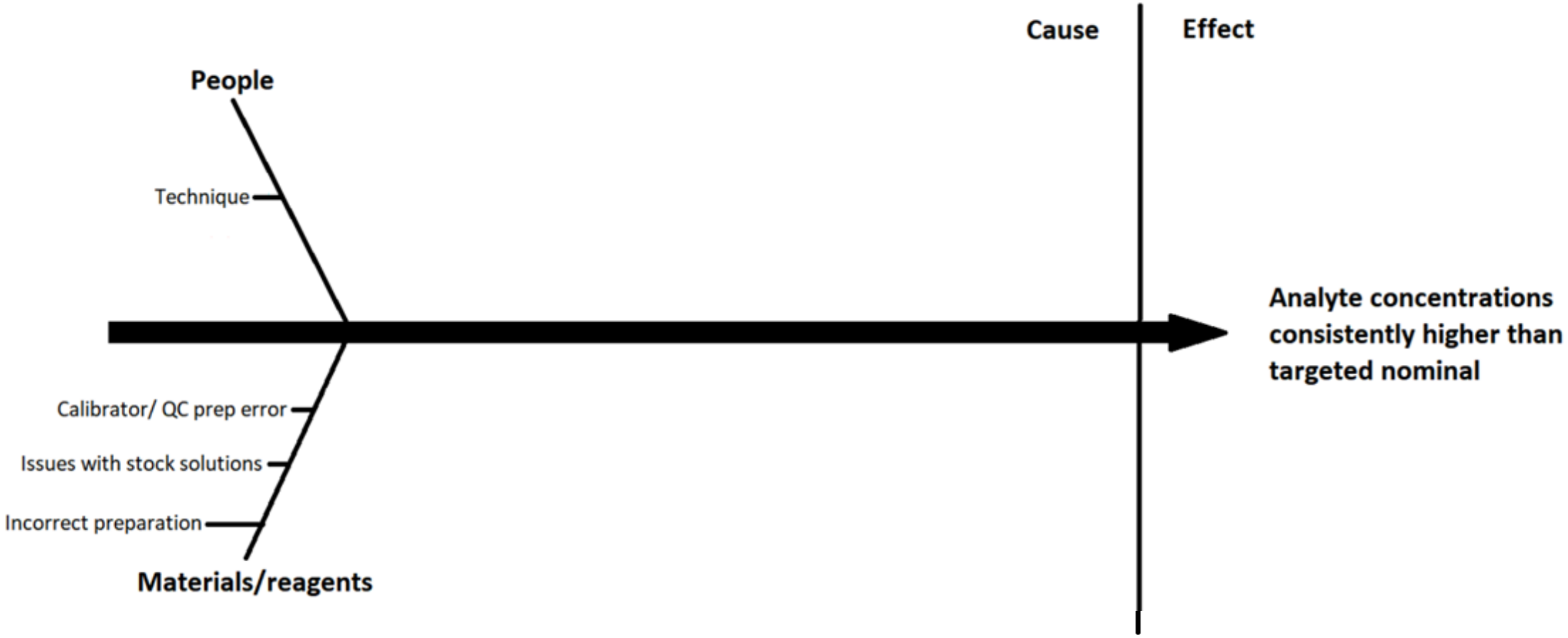
Ruling out potential causes in the form of equipment, method, environment and people, focus was given to the analyte and some investigative testing performed

<u>Analyte (stability & extraction issues)</u>

- **Older (21 day old) test & reference article samples were compared with freshly prepared test & reference article samples, the concentrations were found to be identical**
- **Sample extract showed no precipitate**
- **The assay uses an aggressive digestion technique**
- **Concentration of the analyte was increased, binding was ruled out as a potential cause**

Given these points, issues with the compounds themselves seemed unlikely

Case study – Cause overview 3



Case study – Further investigation

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With no immediate explanation, further investigation was conducted to rule out some other potential causes

This involved two other experienced analysts preparing their own standard solutions from stock and then their own calibrators, run QCs, and test & reference article samples

They then both extracted a run using their own samples, bracketing the calibrators, run QCs and test & reference article samples prepared by the original analyst

Both runs came back with matching calibrators, run QCs and test & reference article samples, of which the test & reference article samples were still above the desired nominal

Case study – Narrowing down the issue

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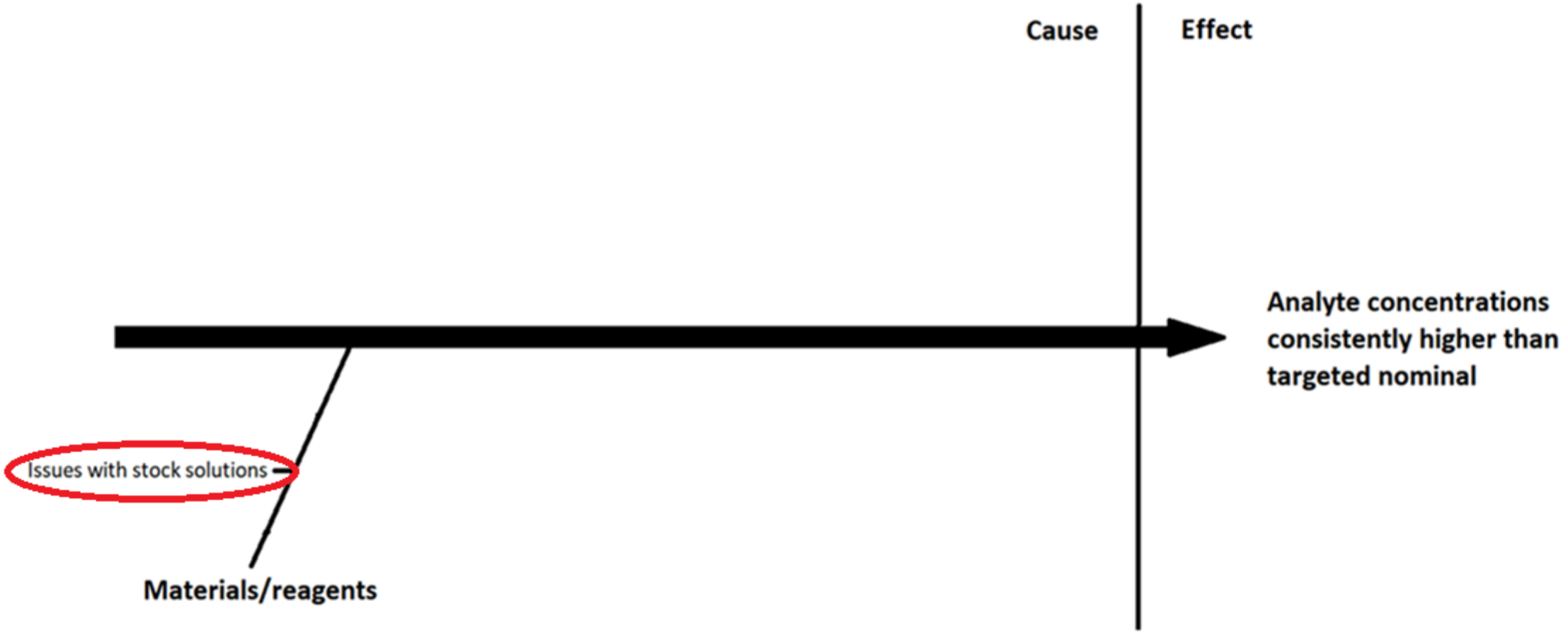
As multiple analysts had all managed to achieve the same results independently, the results of this testing helped eliminate more potential causes, namely:

- **Calibrator & QC solution and sample preparation error**
- **Test and reference article sample preparation error**
- **Analyst technique/experience**

Case study – Cause overview 4



Case study – The point of failure

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Commercial and client provided stock solutions were considered among the least likely causes, as they are tested to confirm purity and all came with detailed COAs

Focus was given to the client provided stock solutions as the commercial stock:

- **Had its purity tested using equally sensitive equipment by the supplier**
- **Additionally it had been used in other on-site studies successfully**

As the client's test and reference article had been tested on less sensitive equipment, a more refined potential cause had arose:

- **The test and reference article had been incorrectly prepared and the concentration underestimated**

Case study – Confirming the cause

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In order to confirm the potential cause, the API form of both the test & reference article was requested and received from the client

Using preparation instructions from the client, stock solutions were prepared in-house and samples prepared from these solutions. These were then analysed

The newly prepared test & reference article samples achieved the desired nominals

Despite the unlikelihood, we had confirmed the test and reference article stock solutions prepared by the client were likely prepared incorrectly. The client was notified and the rest handled from their side

What was learned?

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The use of RCA, in this case the fishbone diagram method, allowed for an efficient and logical way in which to approach finding the <u>why</u> of the assay failure

It enabled for the systematic elimination of potential causes and with proper notation it was easy to go back and confirm the work already performed as well, resulting less complications or unnecessary repetition

A takeaway from this case study, was the reminder that assumptions can be dangerous, as initially it was assumed the failure was:

- Unlikely to be stock solutions (Occam's Razor – the solution is likely the simplest one)
- That by default the issue was on our end, not client side

When looking for the solution, one should remain open minded to all possibilities

The potential of RCA

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In this case study, we did not generate any new data as such, important lessons were still learned

In other situations, the use of RCA when encountering other failures could grant new information and insights on:

- **The behaviours/chemistry of compounds and analytes of interest**
- **Limitations of techniques**
- **Alternative applications for equipment and methodologies**

And the list goes on

In other words, failure can yield its own rewards

Summary

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We are going to fail, it is a fact of life

However with the right tools i.e. RCA, we can understand our failures, learn from them, build on them and share the lessons learned and data gained

By openly discussing and sharing our failures we can help others avoid repeating the same mistakes, optimise their own work and further build upon what was learned

Moving forward together

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By working together we can all contribute to the collective advancement of bioanalysis

But in order to so it is important that we accept and embrace the inevitability of failure in our work and endeavour collectively to normalise failure

It is not always a negative event, but an opportunity as scientists to continue to learn

“It is possible to commit no mistakes and still fail, that is not weakness, that is life”

Acknowledgments

I'd like to thank:

My colleagues at Quotient Sciences

My colleagues on the EBF YSS organising committee

And you, the audience

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Thank you!
Questions?