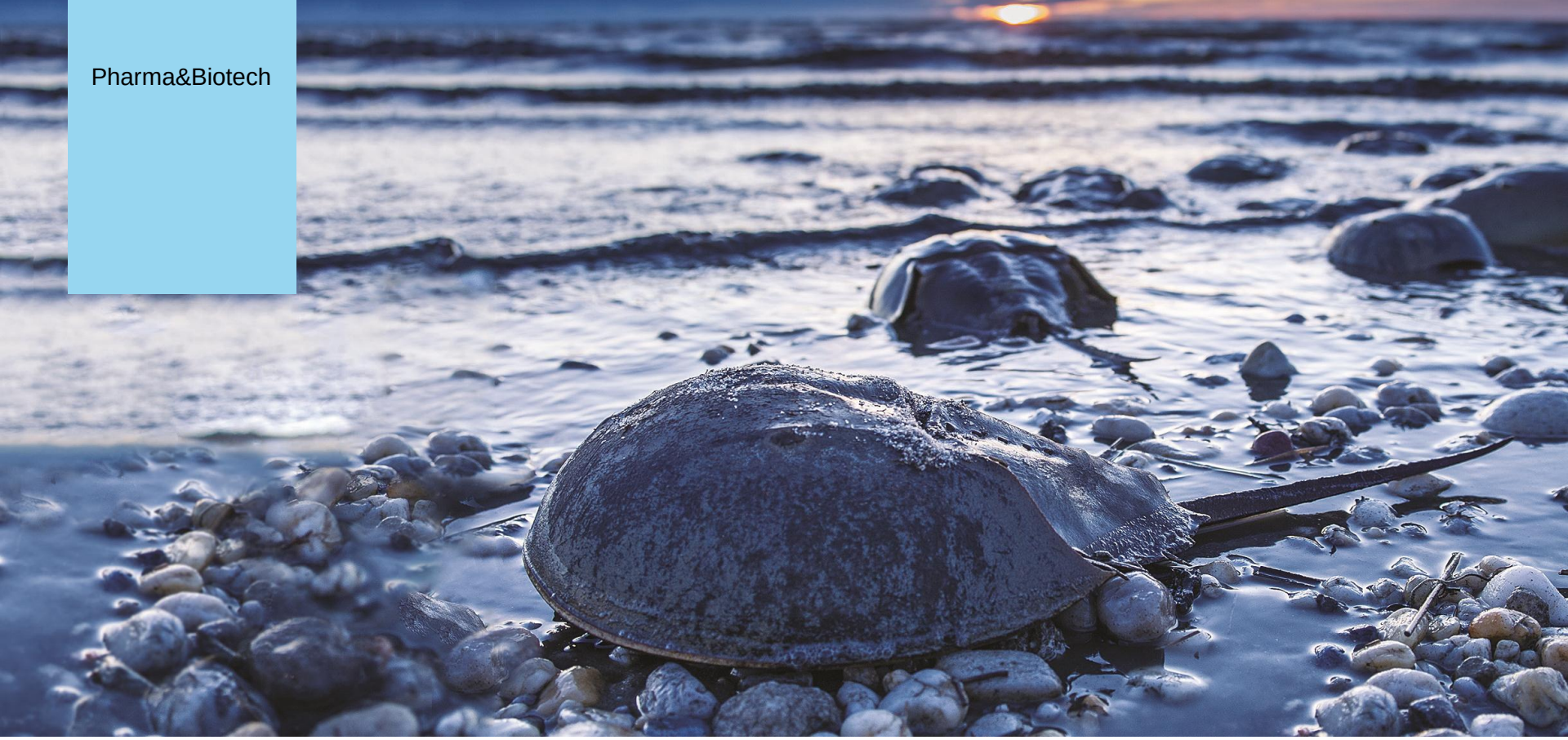
Pharma&Biotech



Conducting Effective OOS or OOT Investigations for Unexpected Results from the BET Assay

Lonza Cologne GmbH, Cologne / 10 May 2013© Lonza

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Dealing with Unexpected Results in Routine Testing

- In a well controlled aseptic production process, the likelihood of product adulteration by endotoxin should be minimal
- This means that the vast majority of results generated in the BET should be either below the Endotoxin Release Limit (ERL) for the product or undetectable i.e. below the detection limit of the assay
- However, unexpected results can and do occur with some frequency in QC laboratories, worldwide

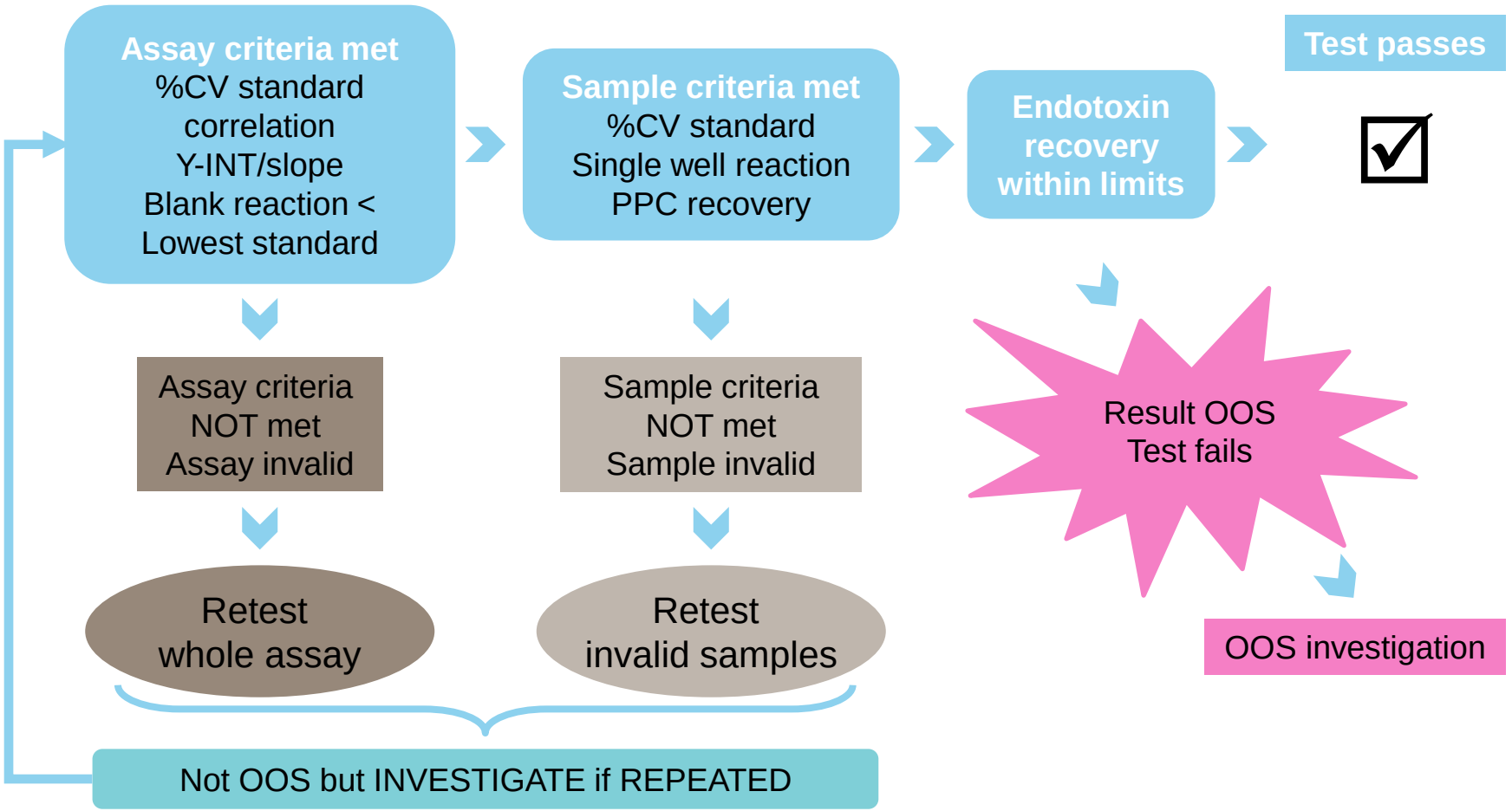
FDA Guidelines on OOS & OOT Results

- OOS (Out of Specification)
  - “All suspect results that fall outside the specification or acceptance criteria established in new drug applications, official compendia, or by the manufacturer”
- OOT (Out of Tolerance)
  - Consideration should equally be applied to results which are atypical and could constitute an increased risk
- *Source*
  - *FDA Guidance for Industry. Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production.*
  - *http://www.fda.gov/cder/guidance/index.htm*

Initial Assessment

- There should be an objective and timely assessment to:
  - Establish likelihood of laboratory error
    - OR
  - Confirm there is an indication of manufacturing process / product problems
  - Assess significance of the result in overall QA program
- The process for making the decision on these key questions must be documented in an approved SOP

BET Assay Assessment Flow Chart



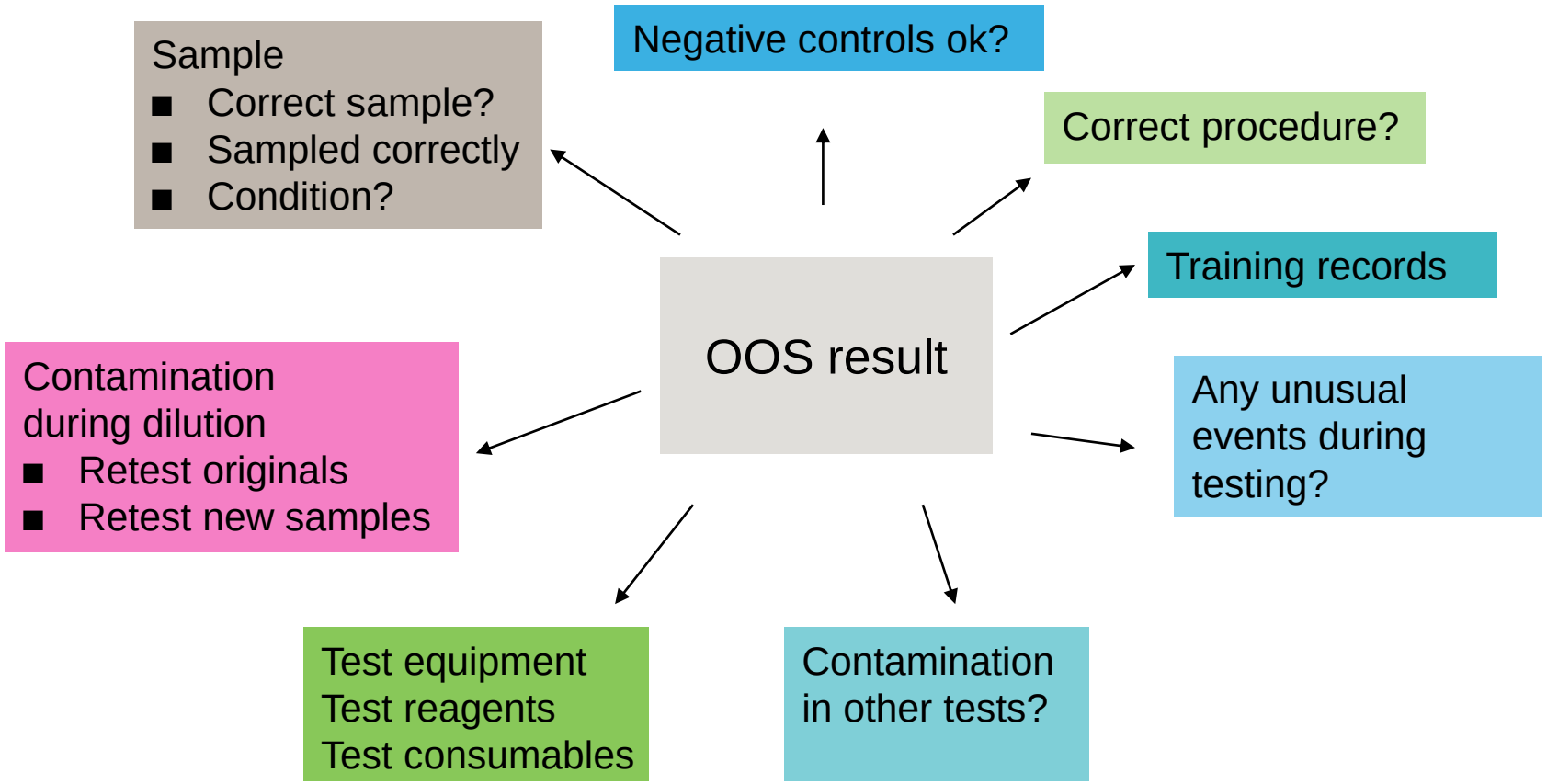
If an OOS Investigation Is Merited

- Report suspect result to QA/Regulatory for assessment
- Notify production of need to investigate process
- An investigation team should be formed
- Start a documented investigation process, as soon as possible
- Make preliminary assessment of effects
- Inform customer services / production of potential consequences

Can the Result Be Attributed to Laboratory Error ?

- Supporting historical data with trend analysis will help
  - Justify the decision making process
  - Suggest Corrective And Preventative Actions (CAPA)
- Working with paper-based reports or excel spreadsheets can be cumbersome
- As kinetic BET assays generate large volumes of data, a database approach is recommended with Structured Query Language capability

Laboratory Error – Potential Causes



A Logical Approach Can Focus the Investigation

- When investigating potential laboratory error, use logic to narrow the field of investigation
- I usually classify issues with kinetic assays into one of three types
  - Likely to cause individual well variations, i.e. one well in error in a pair
  - Likely to cause multiple replicate errors, i.e. duplicate wells are in error
  - Likely to cause multiple well variations (all or several wells on the same plate in error)
- Similarly, you can identify factors that are likely to only affect the standard curve or only likely to affect sample results.
- Doing this will narrow the field of search, when asking questions of the database.

PPC Out-Of-Trend – Situation

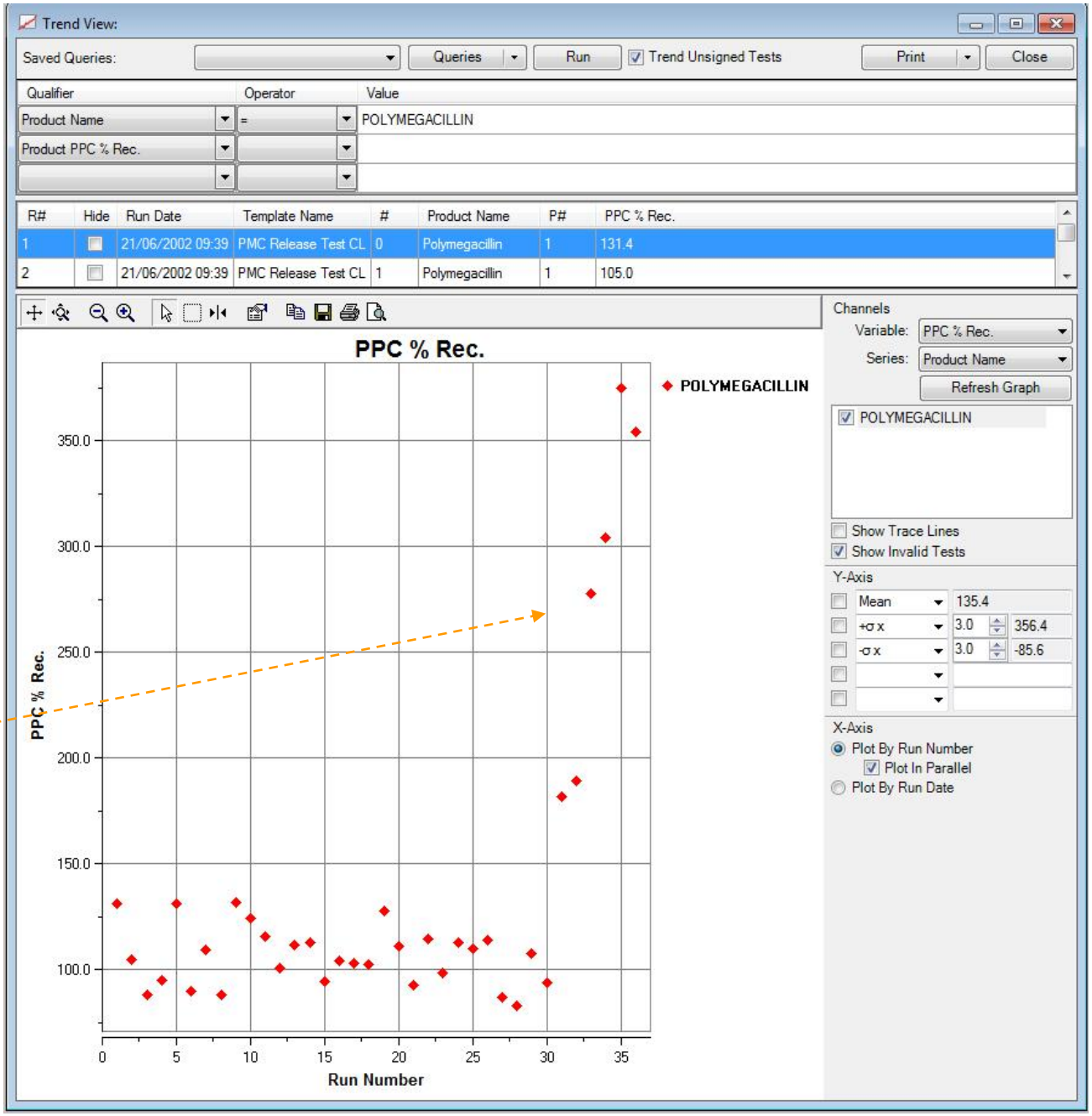
- The following example illustrates the ease and efficiency of investigating OOS or OOT results using trend analysis:
  - Company ‘XYZ’ makes an antibiotic ‘Polymegacillin’
  - PPC recovery percentages are normally consistent but recent assays show a sharp upward trend, with OOS & OOT results
  - Endotoxin results for the unspiked samples appear normal and follow previous trend

Potential Sources of Error in PPC Recovery

- What could be the possible cause(s)?
  - Technician Error?
  - Glucans?
  - Sample contamination?
  - Accessories?
  - Change in product formulation?
- Plan of action?
  - Data Analysis & Trending using the built-in Trend Analysis module of the WinKQCL™ Software

Query qualifiers used

Sharp upward trend for PPC results from assay 31 onwards



Query qualifiers used

5 analysts involved

Trend View:

Saved Queries: | Queries | Run | Trend Unsigned Tests | Print | Close

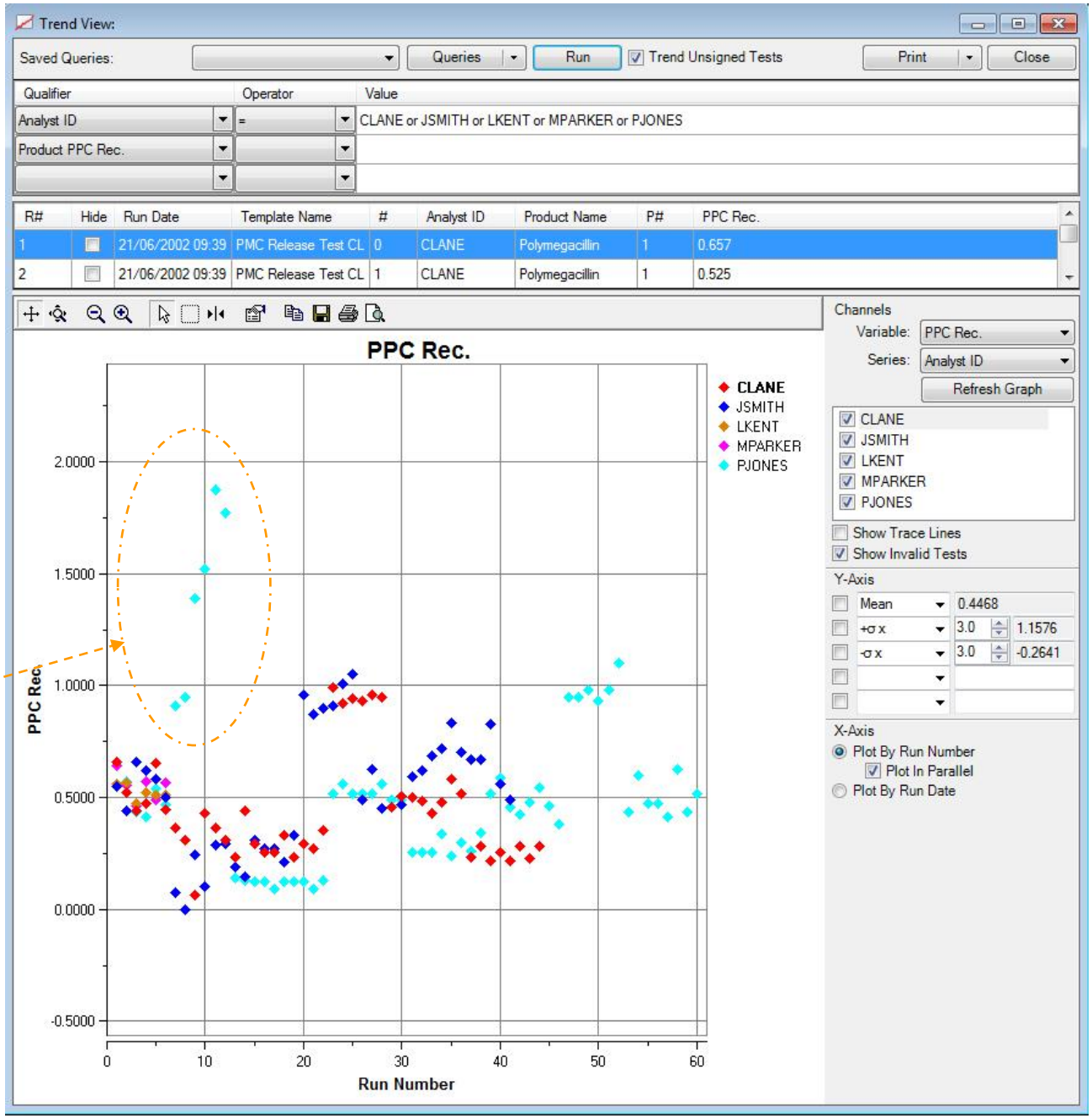
Qualifier	Operator	Value
Analyst ID		
Product Name	=	POLYMEGACILLIN

R#	Run Date	Template Name	#	Analyst ID	Product Name	P#
1	21/06/2002 09:39	PMC Release Test CL	0	CLANE	Polymegacillin	1
2	21/06/2002 09:39	PMC Release Test CL	1	CLANE	Polymegacillin	1
3	21/06/2002 09:39	PMC Release Test CL	2	CLANE	Polymegacillin	1
4	21/06/2002 09:39	PMC Release Test CL	3	CLANE	Polymegacillin	1
5	21/06/2002 09:39	PMC Release Test CL	4	CLANE	Polymegacillin	1
6	21/06/2002 09:39	PMC Release Test CL	5	CLANE	Polymegacillin	1
7	21/06/2002 10:27	PMC Release Test JS	0	JSMITH	Polymegacillin	1
8	21/06/2002 10:27	PMC Release Test JS	1	JSMITH	Polymegacillin	1
9	21/06/2002 10:27	PMC Release Test JS	2	JSMITH	Polymegacillin	1
10	21/06/2002 10:27	PMC Release Test JS	3	JSMITH	Polymegacillin	1
11	21/06/2002 10:27	PMC Release Test JS	4	JSMITH	Polymegacillin	1
12	21/06/2002 10:27	PMC Release Test JS	5	JSMITH	Polymegacillin	1
13	21/06/2002 11:10	PMC Release Test LK	0	LKENT	Polymegacillin	1
14	21/06/2002 11:10	PMC Release Test LK	1	LKENT	Polymegacillin	1
15	21/06/2002 11:10	PMC Release Test LK	2	LKENT	Polymegacillin	1
16	21/06/2002 11:10	PMC Release Test LK	3	LKENT	Polymegacillin	1
17	21/06/2002 11:10	PMC Release Test LK	4	LKENT	Polymegacillin	1
18	21/06/2002 11:10	PMC Release Test LK	5	LKENT	Polymegacillin	1
19	21/06/2002 13:46	PMC Release Test ...	0	MPARKER	Polymegacillin	1
20	21/06/2002 13:46	PMC Release Test ...	1	MPARKER	Polymegacillin	1
21	21/06/2002 13:46	PMC Release Test ...	2	MPARKER	Polymegacillin	1
22	21/06/2002 13:46	PMC Release Test ...	3	MPARKER	Polymegacillin	1
23	21/06/2002 13:46	PMC Release Test ...	4	MPARKER	Polymegacillin	1
24	21/06/2002 13:46	PMC Release Test ...	5	MPARKER	Polymegacillin	1
25	21/06/2002 14:28	PMC Release Test PJ	0	PJONES	Polymegacillin	1
26	21/06/2002 14:28	PMC Release Test PJ	1	PJONES	Polymegacillin	1
27	21/06/2002 14:28	PMC Release Test PJ	2	PJONES	Polymegacillin	1
28	21/06/2002 14:28	PMC Release Test PJ	3	PJONES	Polymegacillin	1
29	21/06/2002 14:28	PMC Release Test PJ	4	PJONES	Polymegacillin	1
30	21/06/2002 14:28	PMC Release Test PJ	5	PJONES	Polymegacillin	1

Query qualifiers used

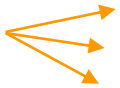
Nearly all OOT PPCs performed by PJONES

Faulty technique?
Contamination?



Isolate items most likely to be involved

e.g. P20 pipettor



Trend View:

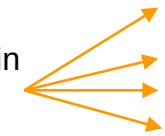
Saved Queries: | Queries | Run | Trend Unsigned Tests | Print | Close

Qualifier	Operator	Value
Product Name	=	POLYMEGACILLIN
Analyst ID		
Accessory Name		

R#	Run Date	Template Name	#	Product Name	P#	Analyst ID	Accessory Name
1	21/06/2002 09:39	PMC Release Test CL	0	Polymegacillin	1	CLANE	13mm Dilution Tubes
2	21/06/2002 09:39	PMC Release Test CL	1	Polymegacillin	1	CLANE	13mm Dilution Tubes
3	21/06/2002 09:39	PMC Release Test CL	2	Polymegacillin	1	CLANE	13mm Dilution Tubes
4	21/06/2002 09:39	PMC Release Test CL	3	Polymegacillin	1	CLANE	13mm Dilution Tubes
5	21/06/2002 09:39	PMC Release Test CL	5	Polymegacillin	1	CLANE	13mm Dilution Tubes
6	21/06/2002 09:39	PMC Release Test CL	4	Polymegacillin	1	CLANE	13mm Dilution Tubes
7	21/06/2002 09:39	PMC Release Test CL	4	Polymegacillin	1	CLANE	MP200 Multipettor
8	21/06/2002 09:39	PMC Release Test CL	5	Polymegacillin	1	CLANE	MP200 Multipettor
9	21/06/2002 09:39	PMC Release Test CL	3	Polymegacillin	1	CLANE	MP200 Multipettor
10	21/06/2002 09:39	PMC Release Test CL	2	Polymegacillin	1	CLANE	MP200 Multipettor
11	21/06/2002 09:39	PMC Release Test CL	1	Polymegacillin	1	CLANE	MP200 Multipettor
12	21/06/2002 09:39	PMC Release Test CL	0	Polymegacillin	1	CLANE	MP200 Multipettor
13	21/06/2002 09:39	PMC Release Test CL	0	Polymegacillin	1	CLANE	P20 Pipettor
14	21/06/2002 09:39	PMC Release Test CL	1	Polymegacillin	1	CLANE	P20 Pipettor
15	21/06/2002 09:39	PMC Release Test CL	2	Polymegacillin	1	CLANE	P20 Pipettor
16	21/06/2002 09:39	PMC Release Test CL	3	Polymegacillin	1	CLANE	P20 Pipettor
17	21/06/2002 09:39	PMC Release Test CL	5	Polymegacillin	1	CLANE	P20 Pipettor
18	21/06/2002 09:39	PMC Release Test CL	4	Polymegacillin	1	CLANE	P20 Pipettor
19	21/06/2002 09:39	PMC Release Test CL	4	Polymegacillin	1	CLANE	P200 Pipettor
20	21/06/2002 09:39	PMC Release Test CL	5	Polymegacillin	1	CLANE	P200 Pipettor
21	21/06/2002 09:39	PMC Release Test CL	3	Polymegacillin	1	CLANE	P200 Pipettor
22	21/06/2002 09:39	PMC Release Test CL	2	Polymegacillin	1	CLANE	P200 Pipettor
23	21/06/2002 09:39	PMC Release Test CL	1	Polymegacillin	1	CLANE	P200 Pipettor
24	21/06/2002 09:39	PMC Release Test CL	0	Polymegacillin	1	CLANE	P200 Pipettor
25	21/06/2002 10:27	PMC Release Test JS	0	Polymegacillin	1	JSMITH	13mm Dilution Tubes
26	21/06/2002 10:27	PMC Release Test JS	1	Polymegacillin	1	JSMITH	13mm Dilution Tubes
27	21/06/2002 10:27	PMC Release Test JS	2	Polymegacillin	1	JSMITH	13mm Dilution Tubes
28	21/06/2002 10:27	PMC Release Test JS	3	Polymegacillin	1	JSMITH	13mm Dilution Tubes
29	21/06/2002 10:27	PMC Release Test JS	5	Polymegacillin	1	JSMITH	13mm Dilution Tubes

Only two P20 units in active use

One unit PIP782 only used by technician PJONES



Trend View:

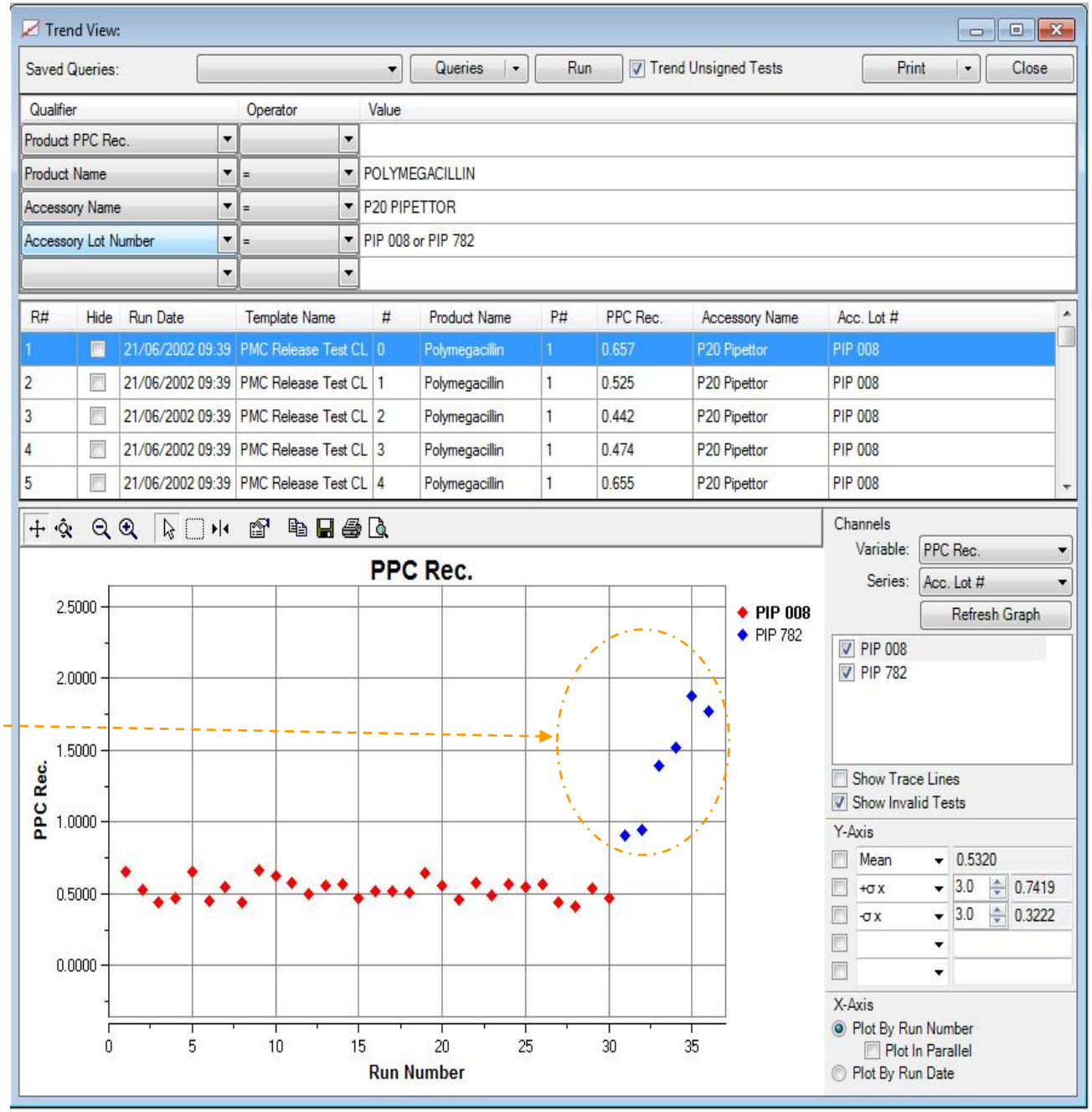
Saved Queries: | Queries | Run | Trend Unsigned Tests | Print | Close

Qualifier	Operator	Value
Product Name	=	POLYMEGACILLIN
Accessory Name	=	P20 PIPETTOR
Accessory Lot Number		
Analyst ID		

R#	Run Date	Template Name	#	Product Name	P#	Accessory Name	Acc. Lot #	Analyst ID
19	21/06/2002 13:46	PMC Release Test ...	0	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
20	21/06/2002 13:46	PMC Release Test ...	1	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
21	21/06/2002 13:46	PMC Release Test ...	2	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
22	21/06/2002 13:46	PMC Release Test ...	3	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
23	21/06/2002 13:46	PMC Release Test ...	4	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
24	21/06/2002 13:46	PMC Release Test ...	5	Polymegacillin	1	P20 Pipettor	PIP 008	MPARKER
25	21/06/2002 14:28	PMC Release Test PJ	0	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
26	21/06/2002 14:28	PMC Release Test PJ	1	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
27	21/06/2002 14:28	PMC Release Test PJ	2	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
28	21/06/2002 14:28	PMC Release Test PJ	3	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
29	21/06/2002 14:28	PMC Release Test PJ	4	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
30	21/06/2002 14:28	PMC Release Test PJ	5	Polymegacillin	1	P20 Pipettor	PIP 008	PJONES
31	21/06/2002 15:30	PMC Release Test PJ	0	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES
32	21/06/2002 15:30	PMC Release Test PJ	1	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES
33	21/06/2002 15:30	PMC Release Test PJ	2	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES
34	21/06/2002 15:30	PMC Release Test PJ	3	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES
35	21/06/2002 15:30	PMC Release Test PJ	4	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES
36	21/06/2002 15:30	PMC Release Test PJ	5	Polymegacillin	1	P20 Pipettor	PIP 782	PJONES

Query qualifiers used

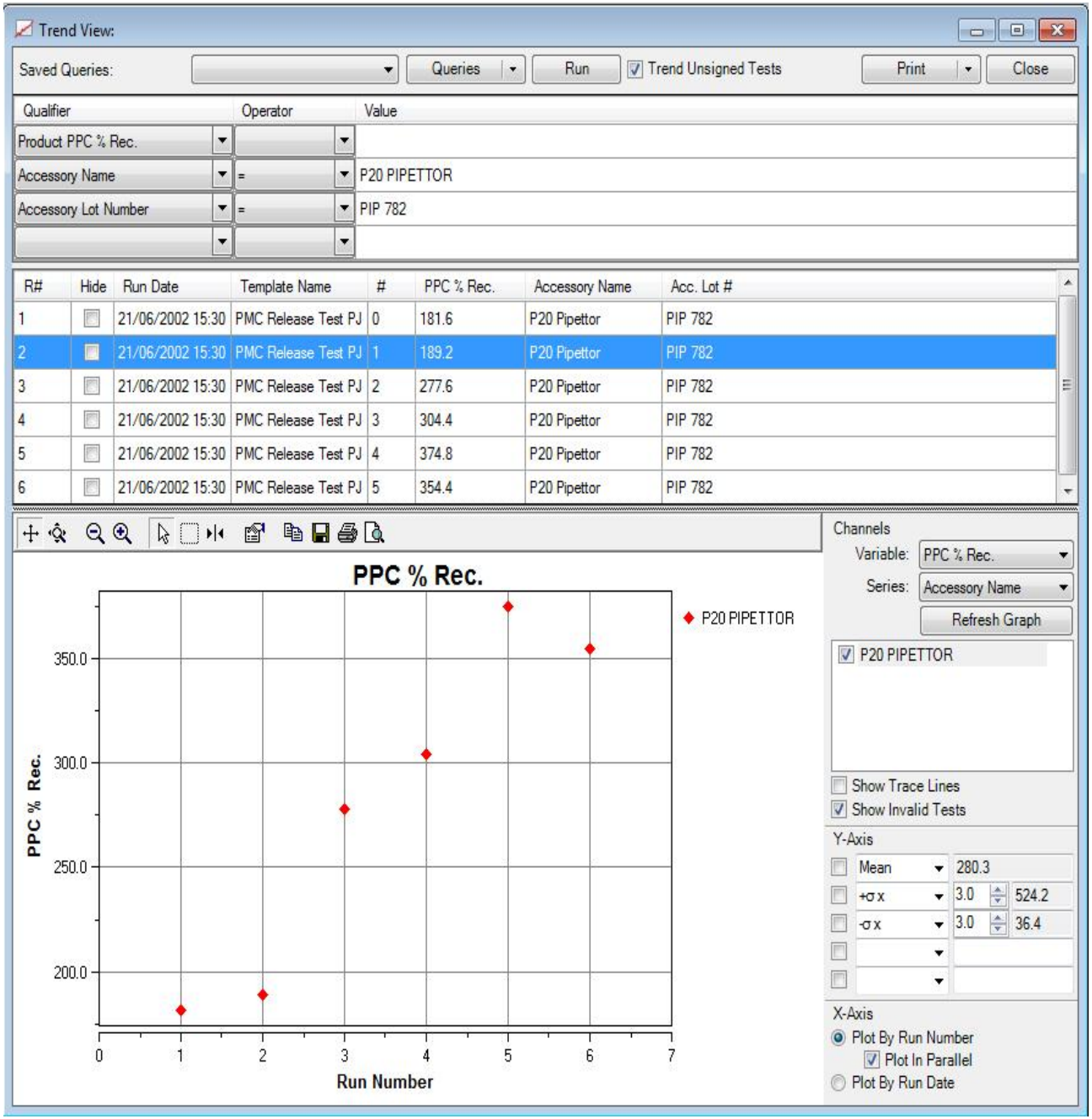
P20 with ID 782 is associated with all high PPC values



Query qualifiers used in this case to highlight the evidence

Evidence clearly indicates a problem with the P20 unit

PIP 782 is the culprit and not technique



Conclusions

- Use of a SQL-database trending program can help identify the cause of unexpected OOS or OOT results
- Such a database should be designed to automatically collect this data, as in the case in Lonza's WinKQCL™ Endotoxin Detection and Analysis Software
- The ability to cross-examine and trend data using query qualifiers helps to rapidly uncover the source(s) of error
- Use of such an integral database can save both time and money, whilst providing documentary evidence for decision processes

Thank You!