



TACS University
E-learning Webinar Series:

*EP 2.2.44 Made Simple
on Teledyne Tekmar's
Fusion*

Agenda

Introduction to
EP 2.2.44 with
Comparison to
USP 643

Fusion
Simplifying Work
flow Software
features for EP
2.2.44 and
Pharmaceutical

Guide to
Running EP
2.2.44

Real World
Results with EP
2.2.44 on the
Fusion

Introduction to EP 2.2.44

Qualify the TOC analysis system through a System Suitability Test

Compares the recovery of 0.500 ppmC sucrose to a of 0.500 ppmC 1,4-benzoquinone

Sucrose is easy to oxidize while 1,4 Benzoquinone is difficult to oxidize

Reagent water must be <100ppb

Compounds responses are a ratio

Response efficiently must be 85% -115%



Response Efficiency EP 2.2.44

$$\frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

r_{ss}

- System Suitability Solution
- 1,4 Benzoquinone Calculated Concentration

r_s

- Standard Solution
- Sucrose Calculated Concentration

R_w

- Reagent water



EP 2.2.44 TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE



EP 2.2.44 Compared to USP 643

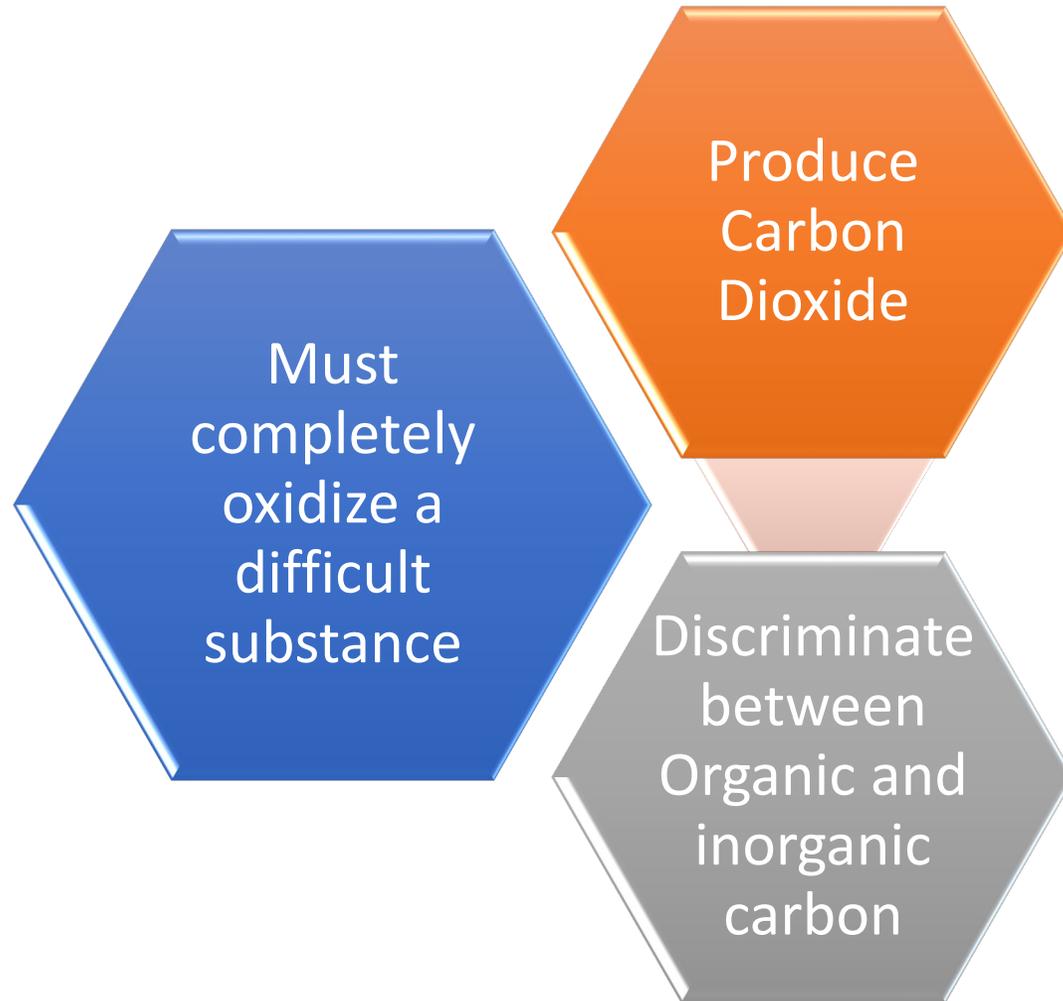
2013 -USP added sterile water section

Sterile water included sterile WFI, sterile PW, sterile water for inhalation, and sterile water for irrigation

Testing of 8ppmC solution of Sucrose and 1,4 Benzoquinone

USP 643 Application Note <http://www.teledynetekmar.com/resources/Application%20Notes/Fusion%20USP%20643%20Bulk%20and%20Sterile%20Water%20Testing.pdf>

EP 2.2.44 Apparatus Requirements



Benefits of TOC over TC-IC

Theoretical

Sample:

TOC = 50 ppb

IC = 100 ppb

TC = 150 ppb

2% error

TC – IC

Error of TC: $0.02 \times 150 = 2.5\text{ppb}$

TC Results = 147.5 to 152.5ppb

Error of IC: $0.02 \times 100 = 2\text{ppb}$

IC Results = 98 to 102 ppb

TC – IC Results Max = $152.5 - 98 = 54.5\text{ppb}$

TC – IC Results Min = $147.5 - 102 = 45.5\text{ppb}$

TC – IC Results Range = 45.5 – 54.5 ppb

TOC (NPOC)

TOC = 50ppb

Error: $0.02 \times 50 = 1\text{ppb}$

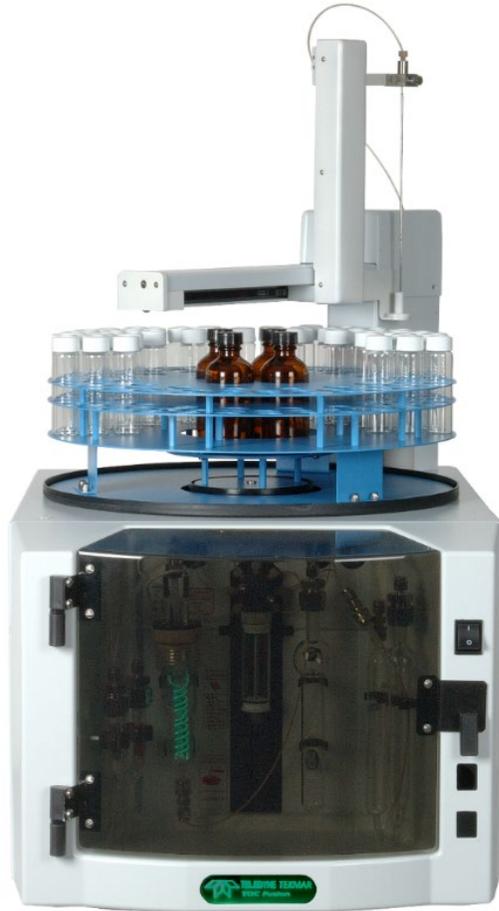
TOC Results Range = 49 – 51ppb

Twice as fast



Less error in
analytical results
with high IC

About the Fusion



UV/Persulfate Oxidation with NDIR Detector

Great sensitivity, accuracy and precision

Many software work flow easing features

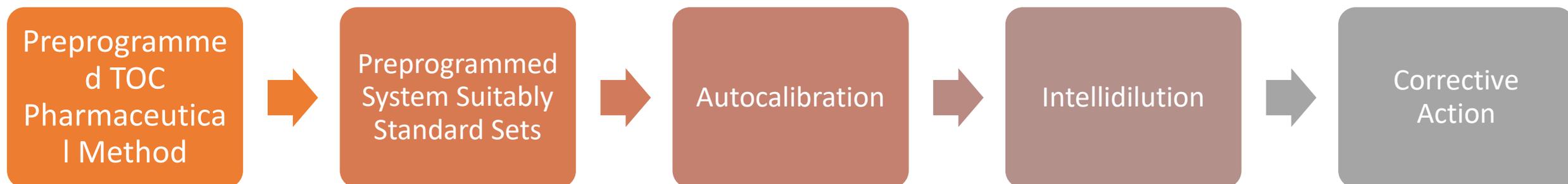


Fusion Software Feature

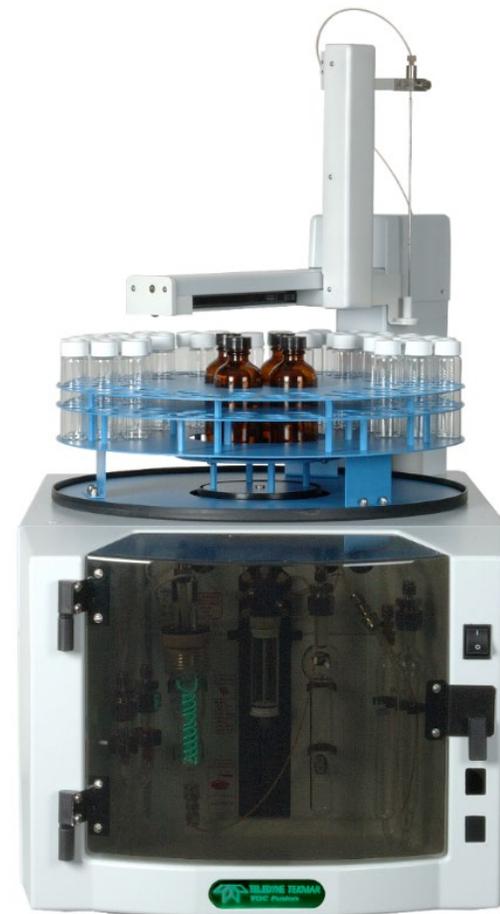
Tools for 21 CFR 11 Compliance



Features



More info: [http://www.teledynetekmar.com/prods/TOC/Documents/MKT-20002_Fusion_TOC_Tools_21CFR11_Compliance_Instruction_Sheet\(REVA\).pdf](http://www.teledynetekmar.com/prods/TOC/Documents/MKT-20002_Fusion_TOC_Tools_21CFR11_Compliance_Instruction_Sheet(REVA).pdf)



Running EP 2.2.44 on the Fusion



Test Criteria

EP 2.2.44

- Reagent Water must be less than 100ppb
- Response Efficiency must be 85-115%

Internal

- Precision represented by %RSD must be less than 5% for all calibration and system suitability standards
- Accuracy must be within 10%
- R2 value must be > 0.999 with 5 calibration points

Standard Preparation Tips

Stock Standard

- 1000ppmC
- 2.125g of KHP weigh per liter

Calibration Standard

- 5ppmC
- 5ml of stock solution per liter

System Suitability Solution

- 0.75 mg of 1,4-benzoquinone per litre

Standard Solution

- 1.19 mg of sucrose per liter

Tip: Method Parameters

Parameter	Value
Sample Volume	9.0 mL
Dilution	1:1*
Acid Volume	0.5 mL
Reagent Volume	0.6 mL
UV Reactor Prerinse	On
UV Reactor Prerinse Volume	10.0
Number of UV Reactor Prerinses	1
IC Spurge Time	0.50 mins
Detector Sweep Flow	500 mL/min
Presparge Time	0.20 mins
System Flow	500 mL/min

Tips: Calibration Curve

Must include a 100ppb point

0.5ppmC should land in the middle

At least 5 points



Tips: Reagent Water Less than 100ppb

ASTM II grade or better



PM and periodically check of water supply



Refresh daily



Run a clean on the system



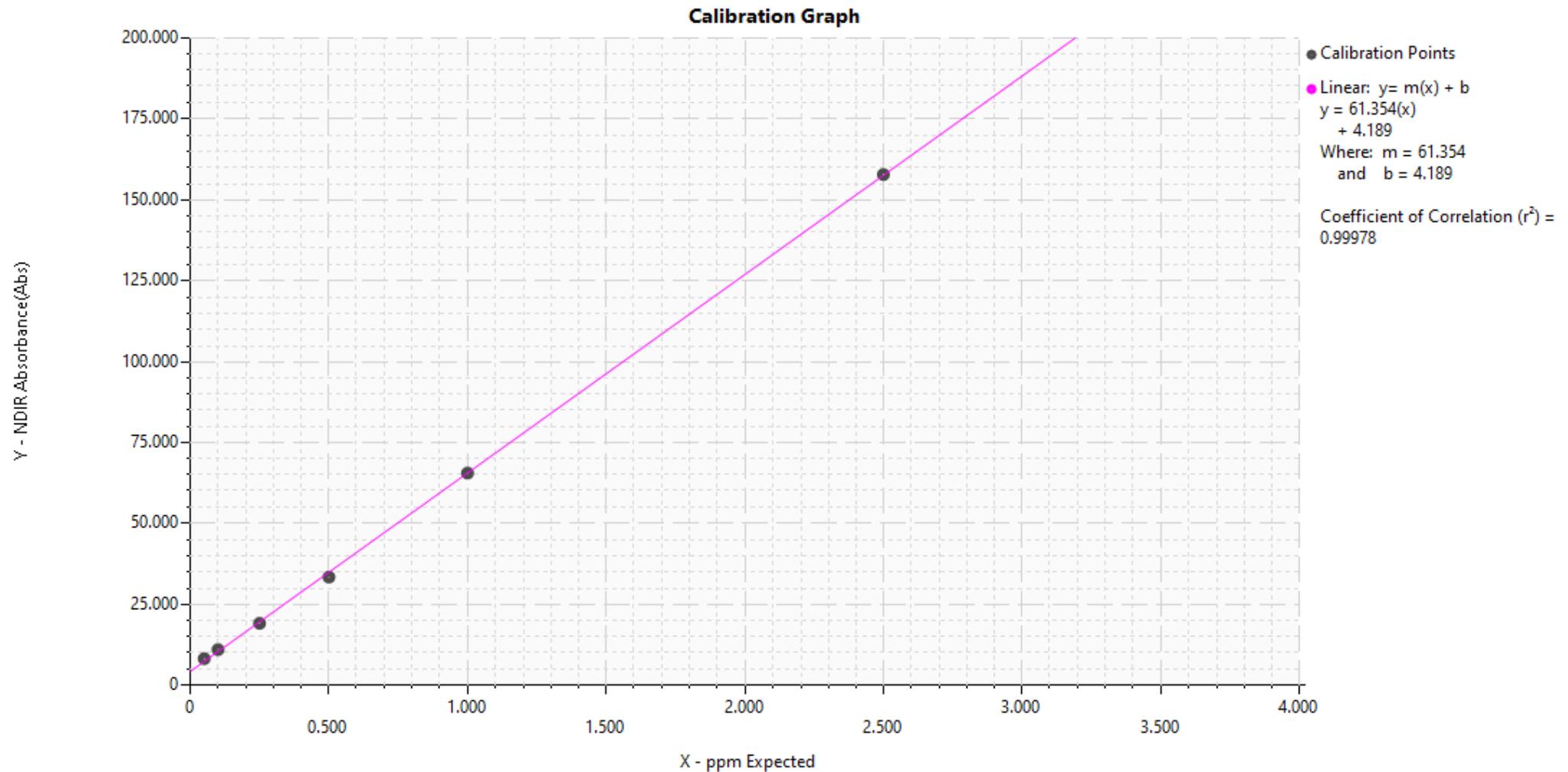
Run a blank



Results



Calibration Results



Calibration Results Continues

pe: Calibration Standard: EP 2.2.44 (Creating calibration TOC Pharmaceutical Water v15 r1)

BAT	Concentration (ppm)	STD Conc	Dil	Sample ID	Result (Abs)	Std. Dev. (Abs)	RSD
5 ppmC	1:50	[TOC] EP 2.2.44 [0.100 ppm]			10.9800	0.3961	3.61%
5 ppmC	1:20	[TOC] EP 2.2.44 [0.250 ppm]			19.1137	0.3378	1.77%
5 ppmC	1:10	[TOC] EP 2.2.44 [0.500 ppm]			33.3997	0.4056	1.21%
5 ppmC	1:5	[TOC] EP 2.2.44 [1.000 ppm]			65.5693	0.3849	0.59%
5 ppmC	1:2	[TOC] EP 2.2.44 [2.500 ppm]			157.8540	3.7627	2.38%



System Suitability Results

Sample Type: System Suitability

	Pos	System Suitability Sample Type	Sample ID	Result	Std. Dev.	RSD
◆	D	Reagent Water	[ReagentWater] USP 643 / EP 2.2.44 [Reagent Water]	0.0403 ppm (PASS)	0.0011 ppm	2.65%
◆	B	Standard Solution	[StandardSolution] USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	0.5660 ppm	0.0120 ppm	2.11%
◆	C	Suitability Solution	[SuitabilitySolution] USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)]	0.5429 ppm	0.0098 ppm	1.81%

Response Efficiency: 95.61%
(Acceptance Criteria 85% to 115%)

Limit Response (Ru): 525.7 ppb

Response Efficiency 95.61%
Precision is less than 5%



System Suitability Results Calculated

$$\frac{r_{ss} - r_w}{r_s - r_w} \times 100$$

$$\text{Response Efficiency} = \frac{r_{ss}-r_w}{r_s-r_w} \times 100$$

$$\text{Response Efficiency} = \frac{(0.5429-0.0403)}{(0.5669-0.0403)} \times 100$$

Response Efficiency = 95.605%

Sample Type: System Suitability

	Pos	System Suitability Sample Type
◆	D	Reagent Water
◆	B	Standard Solution
◆	C	Suitability Solution

Response Efficiency: 95.61%

(Acceptance Criteria 85% to 115%)

System Suitability Accuracy (internal)

- 1,4 Benzoquinone less reagent water

(rss- rw)

$$0.5429 - 0.0403 = 0.5026$$

$$0.5026 / 0.5000 = \mathbf{100.52\% \text{ accurate}}$$

- Sucrose less reagent water

$$(rs- rw) = 0.5660 - 0.0403 = 0.5266$$

$$0.5266 / 0.5000 = \mathbf{105.32\% \text{ accurate}}$$

System Suitability Sample Type	Sample ID	Result
Reagent Water	[ReagentWater] USP 643 / EP 2.2.44 [Reagent Water]	0.0403 ppm (PASS)
Standard Solution	[StandardSolution] USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	0.5660 ppm
Suitability Solution	[SuitabilitySolution] USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)]	0.5429 ppm

Efficiency: 95.61%
(Acceptance Criteria 85% to 115%)

Limit Resp

Limit Response (Ru) Explained

Sample Type: System Suitability

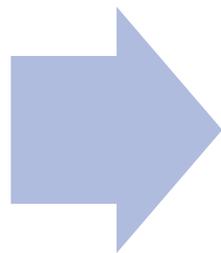
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Response Efficiency: 95.61%
(Acceptance Criteria 85% to 115%)

Limit Response (Ru): 525.7 ppb

Tips for 1,4 Benzoquinone is Coming Out Too Low

Increase the
Prescharge
Time



Increase the
Reagent
Volume



Conclusion

Analytical

- Fusion easily passed EP 2.2.44 criteria
- Passed additional internal analytical criteria

Simplicity

- Fusion has many software features to help users
- Tools for 21 CFR 11



Questions

- Thank you all for attending!
- Please stay healthy and safe!



Works Cited

<http://uspbpep.com/ep50/2.2.44.%20Total%20organic%20carbon%20in%20water%20for%20pharmaceutical%20use.pdf>

https://www.pharmamanufacturing.com/assets/wp_downloads/pdf/GE_SterileWater.PDF

https://en.wikipedia.org/wiki/Water_for_injection

<https://www.fda.gov/validation-cleaning-processes-793>

